IPSO-NITRATION

STUDIES

A thesis

presented for the degree

of

Doctor of Philosophy in Chemistry

in the

University of Canterbury

by

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Christchurch, New Zealand

1985

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ABSTRACT

Nitration of 2,6-dimethyl-4-nitrophenol (40a) with fuming nitric acid gives the pair of C2-epimeric cyclohex-3-enones, (41) and (42), the dihydroxy cyclohex-3-enone[44] and the 2,6-dimethyl-3,4-dinitrophenol (43). Reaction of the nitro phenol (40a) with nitrogen dioxide also gives compounds (41), (42), (43) and (44). The nitration of 2,6-dimethyl-4-bromophenol (40c) with fuming nitric acid (addition of the phenol to the acid) yields both possible C2-epimeric cyclohex-3-enones, (53) and (54), the trinitro cyclohex-3-enone (55) which decomposes to give the dinitro phenol (43), nitro phenol (58) and the 1,4-benzoquinone derivative (59). Nitration of the bromo phenol (40c) in fuming nitric acid (addition of the acid to the phenol) and reaction of the bromo phenol (40c) with nitrogen dioxide both lead to extensive nitrodebromination. The possible reaction pathways for phenols (40a) and (40c) are discussed.

Nitration of 1,2,3,5-tetramethylbenzene (66a) with fuming nitric acid gives the tetramethylnitrobenzene (85), products of side-chain modification (86)-(90), the rearranged 6,6-dimethylcyclohexenones (91), (92), (93) and (94), and 2,3,4,6-tetramethyl ketone derivatives (73)-(76), (95) and (96). Reaction of 2,3,4,6-tetramethylphenol (71) with nitrogen dioxide gives the hydroxy dinitro ketone (72) in addition to the trinitrocyclohexenones (74)-(77) and (82). The possible modes of formation of these compounds are discussed.

Nitration of 1,2,3-trimethyl-4,6-dinitrobenzene (103) with fuming nitric acid gives dimethylpropanedioic acid (108)

(72%), hydroxy dienone (110)(8%) and the substituted benzoic acid (109)(9%). Corresponding nitration of 1,2,4,5-tetramethyl-3,6-dinitrobenzene (117) gives the nitro dicarboxylic acid (119)(33%), dimethylpropanedioic acid (108)(11%) and the substituted benzoic acid (118)(49%). Compounds (108) and (119) are products of reaction pathways involving *ipso*-substitution, followed by methyl migration.

Nitration of 2,4-dimethyl-6-nitrophenol (128) with fuming nitric acid gives two 1,4-benzoquinone derivatives (129) and (130), in addition to the two C4-epimeric cyclohex-2-enones (131) and (132), and a single cyclohex-3-enone (133). In addition, reaction of 2,4-dimethyl-6-nitrophenol (128) with nitrogen dioxide also gives (129), (130), (131), (132) and (133). Comment is made on the reaction mechanism and on the probable mode of conversion of the cyclohex-3-enone (133) to give the C4-epimeric cyclohex-2-enones (131) and (132).

The structures of nine compounds (42), (44), (54), (74), (82), (92), (93), (94) and (96), have been determined unambiguously by single crystal X-ray structure analyses.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Electrophilic Aromatic Substitution

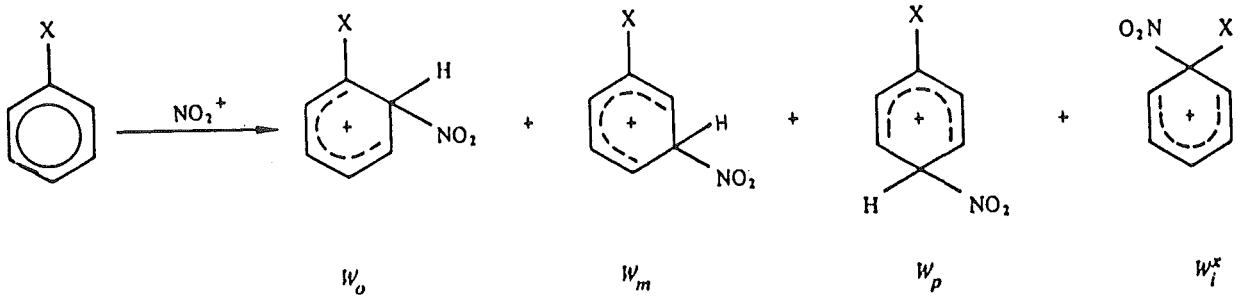
Electrophilic aromatic substitutions have been studied extensively,[1] and the general features of this class of reactions seem well understood. In the case of aromatic nitration reactions the major features may be summarised as follows:[2]

$$ArX + NO_2^+ \rightleftharpoons [ArX \cdot NO_2^+] \rightleftharpoons \overset{+}{Ar}\begin{matrix} X \\ NO_2 \end{matrix} \longrightarrow ArNO_2 + X^+$$

The nitronium ion and the aromatic diffuse together to give an "encounter pair", represented by $[ArX \cdot NO_2^+]$ but of undefined structure. The encounter pair produces relatively unstable σ-complexes (Wheland intermediates) which, by loss of X^+, generate nitro compounds. Depending on the reaction conditions and the structure of the aromatic compound any of the steps may be rate determining. Until recently most work has concerned substitution, where X=H *i.e.* conventional electrophilic substitution.

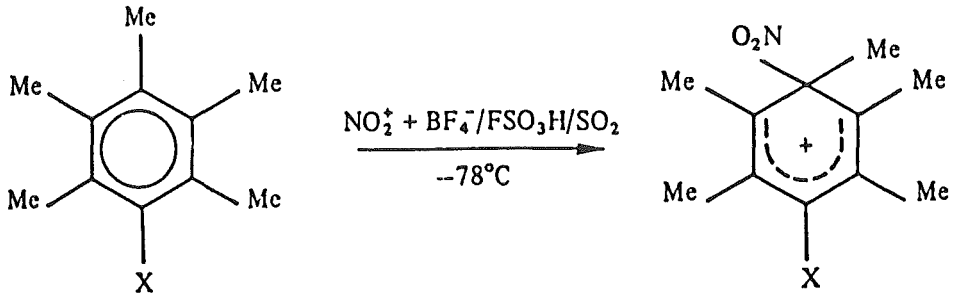
In the electrophilic nitration of monosubstituted benzene derivatives there are two kinds of Wheland intermediate (W_s) formed. Those $(W_o, W_m$ and $W_p)$ formed by nitronium ion attack, at an unsubstituted position, to give conventional substitution products and that (W_i^X) which occurs by attack at a substituted position. In 1971, Perrin and Skinner[3]

introduced the prefix "*ipso*" to denote attack by a reagent at a substituted position on a benzene ring.



Direct observations of the first kind of Wheland intermediate are rare and, generally, their chemistry involves proton loss only. The characteristics, however, of these types of reactions seem well understood.

In contrast, the observation and capture of W_i^X has been possible in some situations. In the absence of bases or nucleophiles some hexasubstituted benzenes give these cations, the structures of which were established from ^1H, ^{19}F and ^{13}C n.m.r. spectroscopy,[4] *e.g.*:-



X = Me, F, Cl, Br

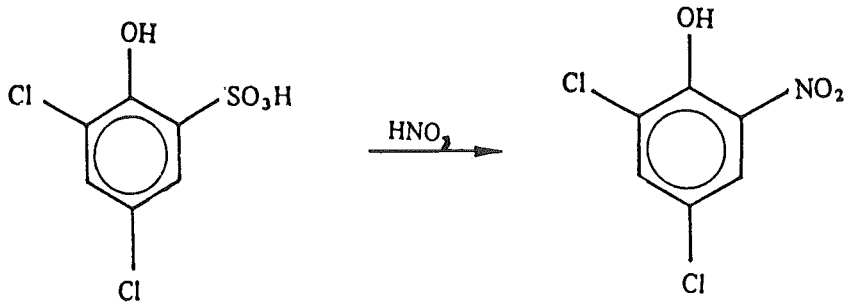
X = Me, F, Cl, Br

1.2 *Ipso* Attack and its Consequences

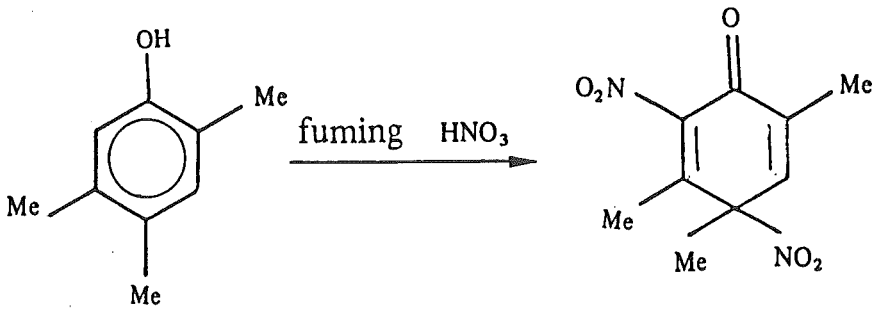
1.2.1 The Early History

Ipso attack is not a new phenomenon. As early as 1871 Armstrong reported[5] the nitrodesulphonation of 2-hydroxy-

3,5-dichlorobenzene sulphonic acid.



Later, von Auwers isolated[6] 2,4,5-trimethyl-4,6-dinitro-cyclohexa-2,5-dienone from the nitration of 2,4,5-trimethyl-phenol in fuming nitric acid.



Subsequently Zincke and Klostermann reported[7] the nitration of 2,3,4,5-tetrabromo-6-methylphenol (1) (Refer Block A)* with fuming nitric acid in acetic acid to give a cyclohexadiene derivative (2). Trituration of this compound (2) with aqueous sodium carbonate solution or addition of water to the nitrating mixture was further reported[7] to give the acyclic derivative (3). Later, Zincke and Breitwieser reported[8] obtaining, from the nitration of 2,4,5-tribromo-3,6-dimethylphenol (4), with fuming nitric acid, the analogous

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* Block A as foldout at end of General Introduction.

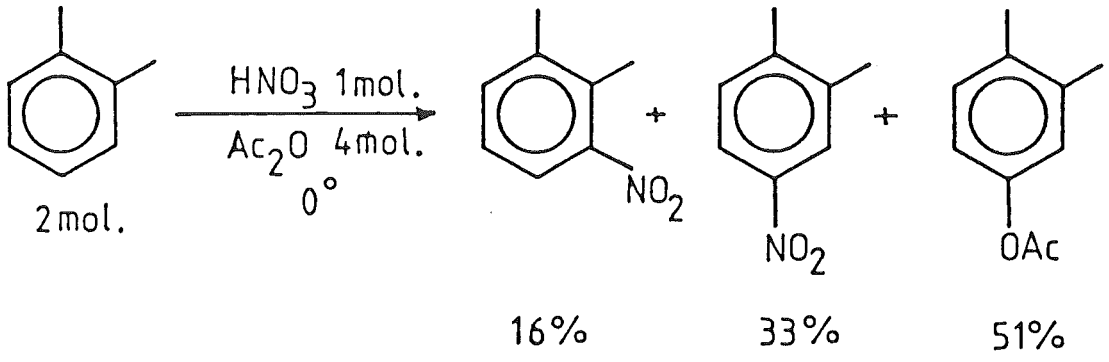
products (5) and (6). Similar results were obtained[9] by Zincke and Preiss for chlorinated 6-methylphenols.

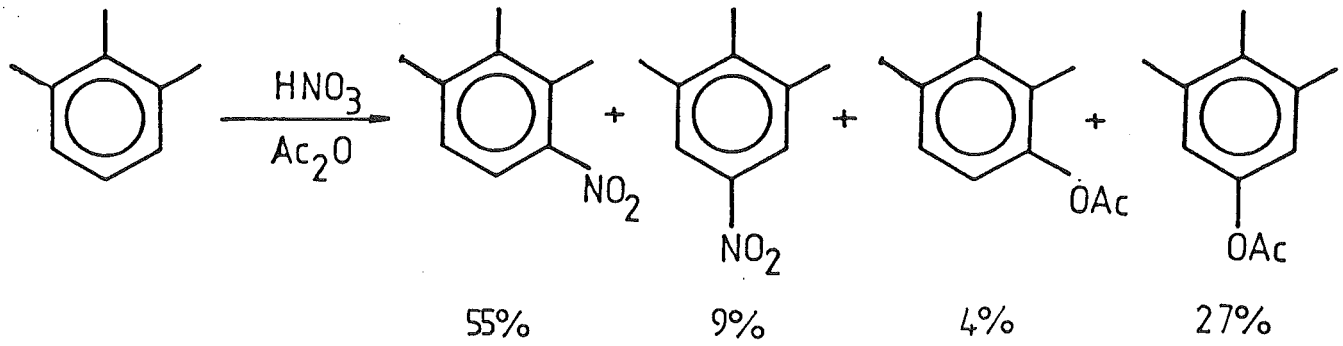
Re-examination of these reactions has shown[10a] (X-ray crystal structure analysis) that the compounds reported by Zincke *et. al.* as (5) and (6) have the structures (7) and (8) respectively (and by analogy[10b] (2) and (3) have the structures (9) and (10)) (Refer Block A).

In addition, examples of *ipso* substitution in which X(X=alkyl,acyl,-SiR_3,-SO_3H, and -N_2Ar) is replaced by a nitro group are common in the literature.[11]

Despite these early examples of *ipso* nitrations, and the long history of aromatic halogenations requiring *ipso* attack for their rationalisation,[12] it was generally thought that aromatic nitration reactions could be explained in terms of conventional *ortho, meta* and *para* attack.

It was not until 1961 that interest in the area of *ipso* substitution was reawakened. Fischer *et. al.* reported[13a] that the nitration of *o*-xylene in nitric acid and acetic anhydride yielded 3,4-dimethylphenyl acetate as the major product (51%) in addition to conventional nitration products. A significant feature of this study was exclusion of alkali from the work-up procedure. The reaction mixture was poured into water, and the product extracted with ether which was then washed several times with water before drying over magnesium sulphate. Subsequently, nitration of hemimellitene, under identical conditions, yielded the 4-acetoxy- and 5-acetoxy- hemimellitenes.[13b]

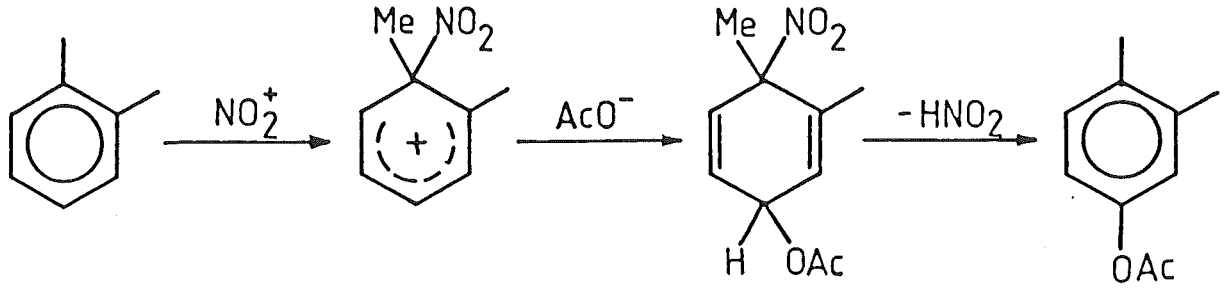




From kinetic studies it was shown that the reaction rate of acetoxylation was independent of the concentration of aromatic substrate, although the ratio of nitration to acetoxylation was substrate dependent.

It was originally thought that the acetoxylating species was protonated acetyl nitrate which on reaction would release nitrous acid. This proposal was consistent with the formation of nitrite in approximately equivalent quantities to the extent of acetoxylation.

The information obtained[13b] was, of course, also consistent with capture of the initially formed Wheland intermediate by acetate ion and subsequent elimination of nitrous acid to give the aryl acetate product.

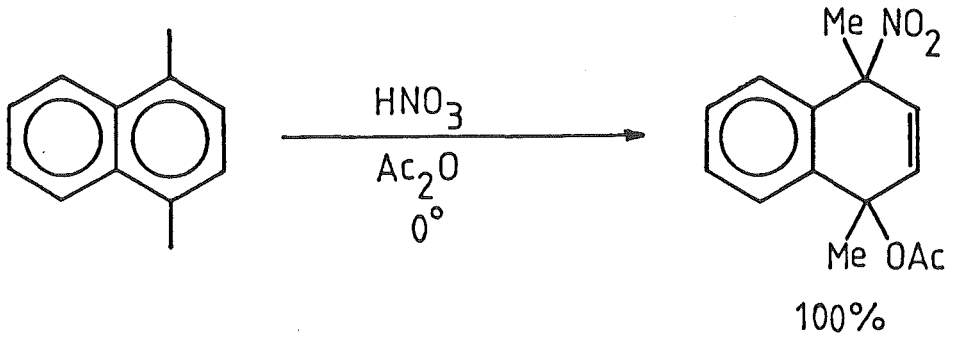


The next major advance in this field was made some ten years after the initial observation of acetoxylation in the nitration of methylbenzenes with nitric acid in acetic anhydride mixtures. In 1970 the isolation of the stereoisomeric adducts

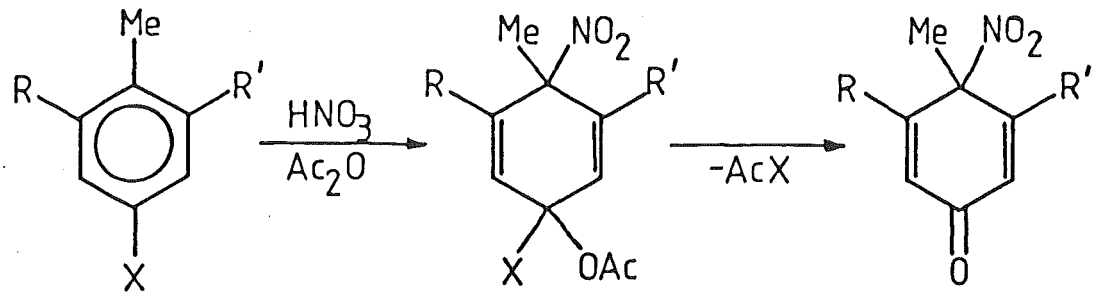
from the nitration of *o*-xylene with nitric acid in acetic anhydride was reported.[14] The significant difference in experimental procedure was in avoiding contact of the adducts, above, with aqueous acid. In aqueous acid the adducts decomposed to give 3,4-dimethylphenyl acetate with the loss of the nitrous acid. Similar products were obtained

for a number of aromatic substrates, mainly by Fischer and his co-workers.[15] In most cases both diastereoisomers were obtained, indicating a two-step process in which initial *ipso* attack is followed by capture of W_i^X, by acetate, at the *para* position.

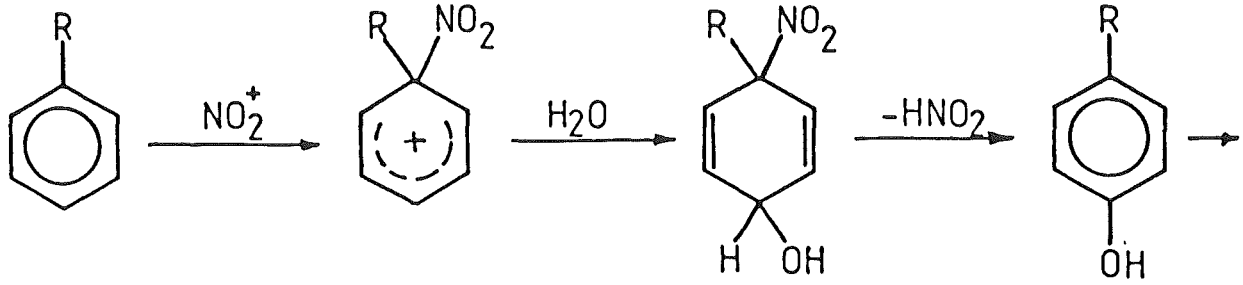
The proportion of conventional nitration to nitro-acetate formation, which remains constant under different conditions, gives important information about positional reactivities in the aromatic substrate.[16] The need for stabilisation of the Wheland intermediate explains the low extent of acetoxylation in toluene. In contrast nitration of 1,4-dimethylnaphthalene yields the nitro-acetate adduct exclusively.[17]



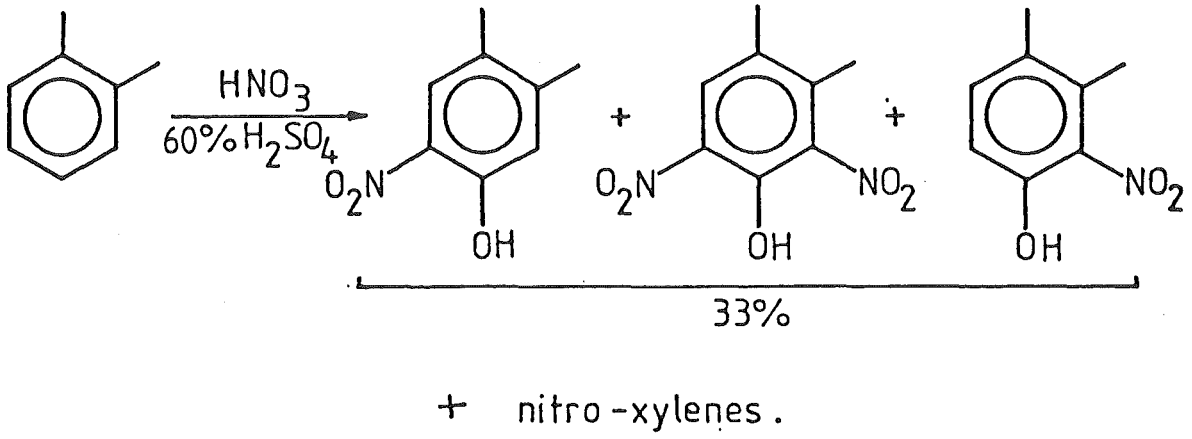
In some cases the nitro-acetate adducts can react further to give dienones, the yield of dienone being dependent on the nature of the substituents X,R and R'.[18]



The *ipso* Wheland intermediates formed can also react with water to give adducts which rearrange readily to phenols by loss of nitrous acid.



For example, the nitration of *o*-xylene by nitric acid in 60% sulphuric acid gives a 33% yield of mono- and dinitro-3,4-dimethylphenols.[19]



1.2.2 Migration of the Nitro Group

The Wheland intermediates W_i^X's formed as a consequence of *ipso* nitration, are capable of rearrangement *via* migration of the nitro group or, less commonly, by migration of X.

Three modes of migration may be recognised, each with differing consequences, and they may be characterised as

(i) intramolecular, (ii) extramolecular, and (iii) intermolecular migration.

(i) Intramolecular migration refers to a process in which the nitro group is never sufficiently free of the carbon structure to do other than move to a position adjacent to the *ipso* position (1,2-migration).

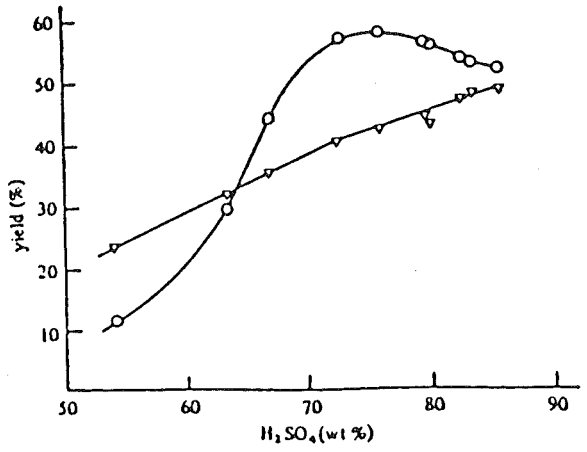
(ii) Extramolecular migration occurs when the nitro group is able to distinguish and select between ring positions, but is unable to leave the encounter pair.

(iii) In intermolecular migration the *ipso* nitro group leaves its ring position and escapes, from its encounter pair, into the solvent. There it may react with carbon structures other than the one that it left.

Characteristically, extramolecular migration occurs when the nitration producing W_i^X proceeds at the encounter rate and intermolecular migration when it is slower than the encounter rate.

Intramolecular Migration

Nitration of *o*-xylene in sulphuric acid gives 3- and 4-nitro-*o*-xylenes in yields which are dependent upon the acidity.[19]



Nitration of *o*-xylene. Yields of 3-nitro (circles) and 4-nitro-*o*-xylene (triangles) as percentages of the starting material.

Scheme 1* outlines the proposed mechanism.[20] Myhre suggested that at low acidities W_i^{Me} was captured by water, but with increasing acidity 1,2-migration of the nitro group became more important. Solvolysis of the nitro-acetate adduct (Scheme 1) gave only 3-nitro-*o*-xylene and 3,4-dimethylphenol, demonstrating that return to the encounter pair - which is necessary to produce 4-nitro-*o*-xylene - does not compete with 1,2-migration of the nitro group on capture of W_i^{Me} by water.

There are many examples of 1,2-migration of the nitro group in W_i^{R}, s generated by solvolysis of the nitro-acetate adducts.[21] Similarly, reactions are known which, though formally 1,3 shifts, are best regarded as repeated 1,2 shifts.[21c,d,e]

Extramolecular Migration

Extramolecular 1,3-migration of a nitro group was first proposed to explain the formation of nitrophenols in the nitration of anisole derivatives.[22,23] The nitration of 4-methylanisole in sulphuric acid gives 4-methyl-2-nitrophenol as well as 4-methyl-2-nitroanisole.[22] The proposed mechanism, illustrated in Scheme 2, involves initial formation of an encounter pair to produce both conventional and *ipso* Wheland intermediates. The nitrocyclohexa-2,5-dienone shown, which forms and decays during the reaction, is also produced in the nitration of *p*-cresol.[24] In strong acid the conjugate acid of the 4-nitrocyclohexa-2,5-dienone rearranges to give the 2-nitrophenol *via* dissociation to an

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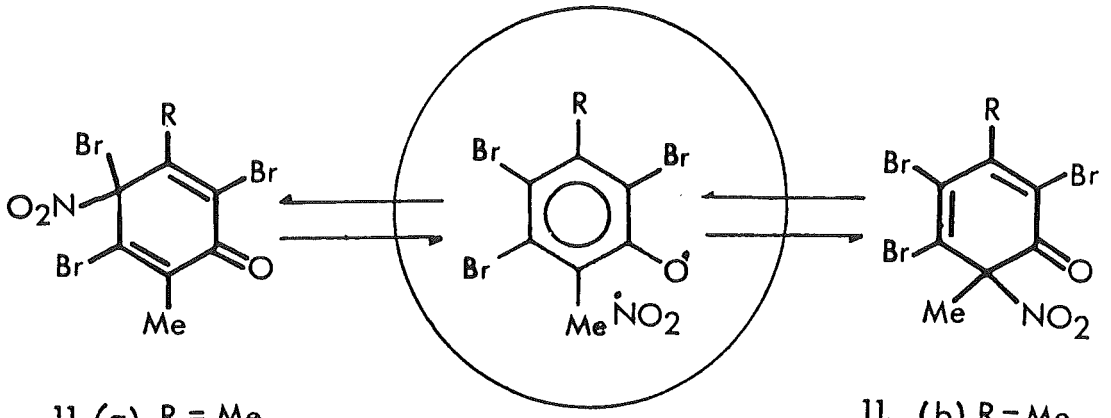
* Schemes 1-8 as foldouts at the end of the General Introduction.

encounter pair and re-nitration. This mechanism is consistent with nitration of *p*-cresol and *p*-methylanisole at the encounter rate. In contast, *p*-chloroanisole reacts more slowly than the encounter limit and gives either 4-chloro-2-nitrophenol and 4-chloro-2-nitroanisole[3,25] or 4-chloro-2,6-dinitrophenol only,[26] depending on the concentration effects. 4-Chlorophenol was detected during the course of the reaction, it having "leaked" from the encounter pair. Studies using $H_2{}^{18}O$ enriched mixtures confirm these proposals.[27]

Of special relevance to the work presented in the main part of this thesis is the extramolecular migration and rearrangement of 4-nitrocyclohexa-2,5-dienones. These compounds rearrange, in the absence of *ortho*-substitution to give *o*-nitrophenols.[18a,b] For example, 4-methyl-, 3,4-dimethyl- and 3,4,5-trimethyl-4-nitrocyclohexa-2,5-dienones gives the corresponding *o*-nitrophenols in hexane, acetic acid, ethanol, water and dimethyl sulphoxide. This conversion has been shown to proceed *via* the radical dissociation-recombination mechanism, outlined in Scheme 3, with some leakage of radicals, from the solvent cage.[18c]

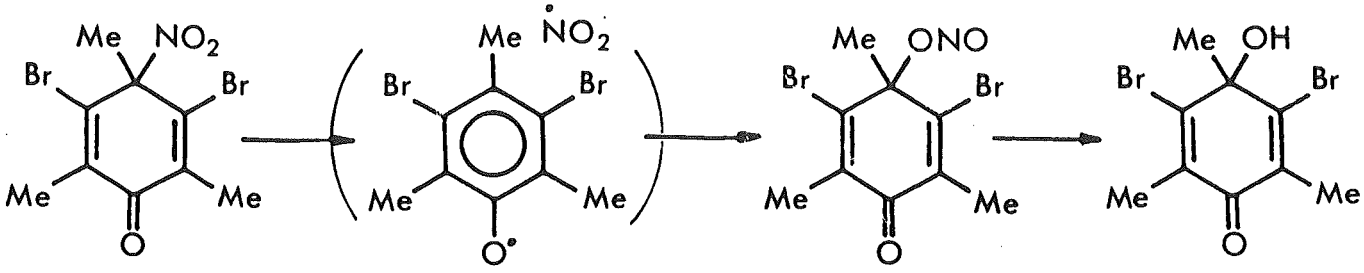
It appears that this radical dissociation-recombination mechanism operates also when the *ortho*-positions are substituted. For the 4-nitrodienones (11a) and (12a) it is possible to establish an equilibrium with their 6-nitro-dienones (11b) and (12b).[28]



11. (a) R = Me
12. (a) R = Br

11. (b) R = Me
12. (b) R = Br

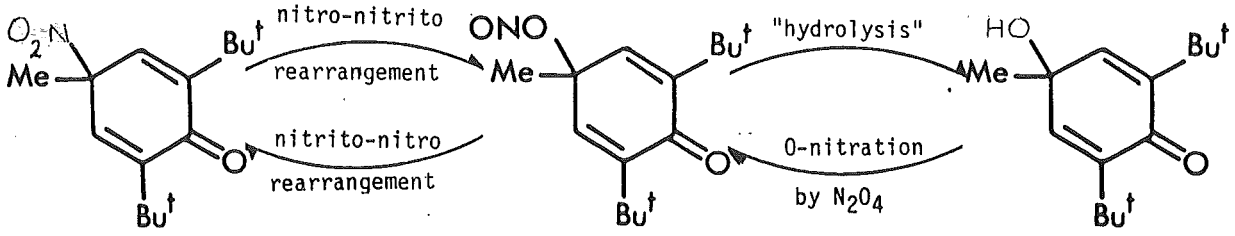
In some cases the 4-nitro-dienones rearrange to give 4- and/or 6-hydroxydienones. For examples, 3,5-dibromo-2,4,6-trimethyl-4-nitrocyclohexa-2,5-dienone rearranges slowly, in chloroform at 30°, to give the corresponding 4-hydroxy dienone.[29] This 4-hydroxy dienone is thought to be formed *via* the recombination of the radical pair to give the intermediate 4-nitrito dienone.



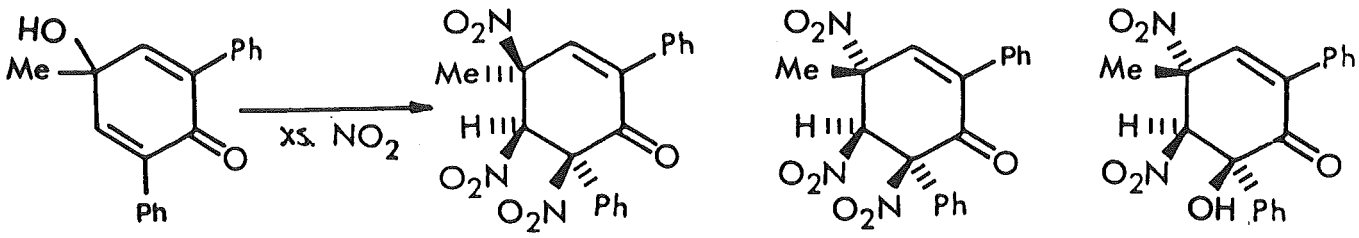
The rearrangement of 2,3,5,6-tetrachloro-4-methyl-4-nitrocyclohexa-2,5-dienone, in chloroform, gives a mixture (c.2:3) of 3,4,6-trichloro-5-methyl-1,2-benzoquinone and 2,3,5,6-tetrachloro-4-hydroxy-4-methylcyclohexa-2,5-dienone.[29] Addition of hydroquinone to the reaction resulted in formation of 2,3,5,6-tetrachloro-4-methylphenol as the major product.[29] These results are consistent with the mechanism

proposed in Scheme 4. Formation of the 4-hydroxy dienone presumably occurs *via* the 4-nitrito dienone intermediate. The 1,2-benzoquinone is probably formed by loss of the elements of NOCl from the 6-nitrito dienone. Whether the 6-nitrito dienone is formed directly, by recombination of the radical pair, or through the nitro-nitrito rearrangement of the 6-nitro dienone is not clear from the information available.

In all of the examples presented hydroxy dienones are formed from nitro dienones by initial nitro-nitrito rearrangement to yield nitrito dienones which, on hydrolysis give the corresponding hydroxy dienones. Recently it has been demonstrated that this reaction sequence may be reversible under certain reaction conditions.



Reaction of 4-hydroxy-4-methyl-2,6-di-t-butyl-cyclohexa-2,5-dienone with excess nitrogen dioxide in benzene solution forms the corresponding 4-nitro dienone in high yield.[30] Similarly 4-hydroxy-4-methyl-2,6-diphenyl-cyclohexa-2,5-dienone reacts with nitrogen dioxide in benzene solution to give the following 4-nitro compounds as well as the expected 4-hydroxy compounds.[30]



These latter results also require a conversion of a 4-hydroxy dienone into a 4-nitro dienone as a crucial reaction step.

1.2.3 *Ipso* Substitution

Ipso-substitution, mentioned earlier, is often included in the description "anomolous nitration",[31] and occurs in cases where it is possible to displace the group *ipso* to the nitro function.

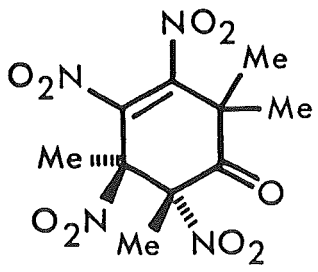
The main area of *ipso*-substitution considered in this work is nitrodebromination. Apparent nitrodebrominations are common in the early literature.[31] Many of these reactions involve very reactive compounds such as brominated phenols or the corresponding ethers.

The nitration of *p*-chloroanisole, discussed previously, proceeds mainly by demethoxylation and subsequent nitro-group migration. With *p*-bromoanisole, nitrodebromination is an added complication.[3,25] Nitration in aqueous acetic acid in the presence of urea gave 4-bromo-2-nitroanisole, *p*-nitroanisole, 2,4-dibromoanisole, *p*-nitrophenol and 2-bromo-4-nitrophenol.[3] Scheme 5 outlines the primary processes thought to be operating. Results indicate that the W_i^{Br} formed, after demethoxylation, can be either nitrodebrominated to give *p*-nitrophenol or bromodenitrated to give after renitration, 4-bromo-2-nitrophenol. In acetic acid W_i^{Br} evidently always loses bromo, rather than nitro, as no

4-bromo-2-nitrophenol is formed.[3]

1.2.4 Methyl Group Migration

There are few reports in the literature citing methyl group migration, consequent upon *ipso* nitronium ion attack at C-Me. In 1972 Suzuki and Nakamura reported,[32] the nitration of 1,2,3,4-tetramethyl-5,6-dinitrobenzene to give a single tetramethyltetranitrocyclohex-3-enone compound (13). This compound (13) was further reported[32] to yield 2,3,6,6-tetramethyl-4,5-dinitrocyclohexa-2,4-dienone (14) by loss of nitrogen dioxide.



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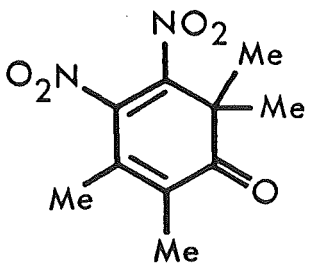
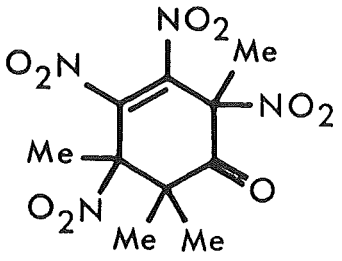


(14)

Although structures (13) and (14) were consistent with spectroscopic data,[32] the alternative tetramethyl-tetranitrocyclohex-3-enone structures (15) and (16) and the tetramethyldinitrocyclohexa-2,4-dienone structure (17) could not be excluded, with confidence, on the published evidence. In addition the mechanistic rationalisation (Scheme 6) proposed by Suzuki and Nakamura[32] required the formation of an unstable cationic product in the methyl migration step.



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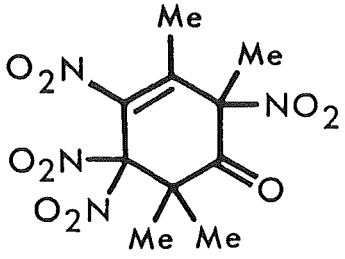
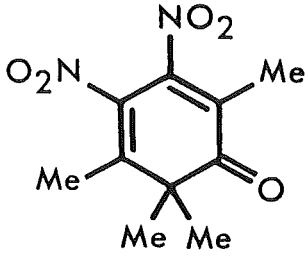
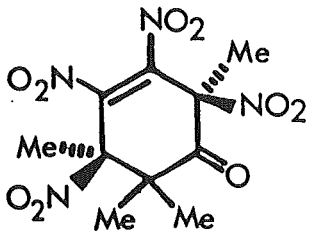


(16)

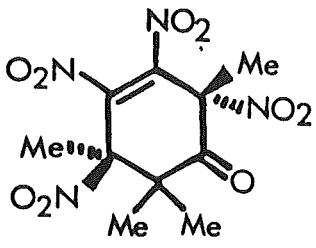


(17)

In 1982 Gray *et. al.* re-examined the nitration of 1,2,3,4-tetramethyl-5,6-dinitrobenzene. They were able to isolate, in high yield, two compounds, (18) and (19). Structural assignments for these two compounds were made on the basis of (i) an X-ray crystal structure of the minor product (18), (ii) their common conversion into the dinitro dienone (17), and (iii) the close similarity of their spectroscopic data.[33] The isomeric ketones, (18) and (19), could also be generated by the addition of nitrogen dioxide to the dinitro dienone (17).



(18)



(19)

Scheme 7 outlines a likely reaction mechanism for the formation of the two isomeric tetramethyltetranitro-cyclohex-3-enones (18) and (19). Nitronium ion attack

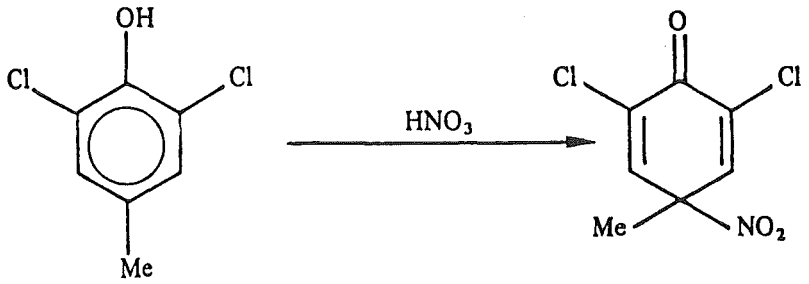
at the most activated ring position gives the *ipso* Wheland intermediate. Subsequent rearrangement through the nitrito derivative then gives rise to the dinitro dienone (17). Homolytic two-step 1,4-addition of nitrogen dioxide to the dinitro dienone (17) then yields the observed cyclohex-3-enones (18) and (19).

1.2.5 Substituent Modification

There are two important types of substituent modification. One type involves a hydroxyl group *ortho* or *para* to the *ipso*-position which loses its proton to form a carbonyl function. Some methoxyl groups can be included in this discussion. The other major category involves an alkyl group, which can be modified in a number of different ways.

Hydroxyl and Methoxyl Groups

One of the earliest reported[34] examples of nitrodienone formation from a phenol is given below.



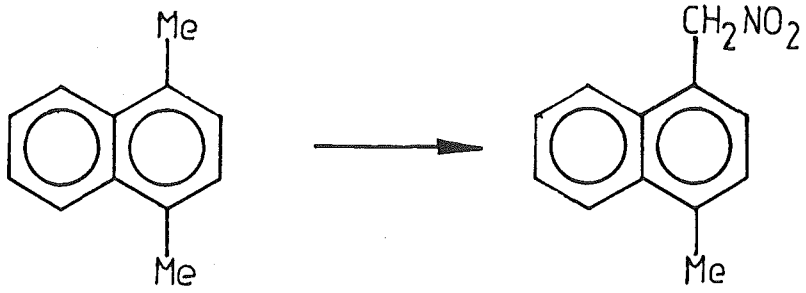
In fact variously substituted *p*-cresols,[35] as well as derivatives of *p*-ethyl- and *p*-t-butyl-phenol, have been shown[36] to react in this way. The formation of phenols

from *o*- and *p*-methylanisole and from pentamethylanisole[35a] are assumed to proceed by nucleophilic demethyoxylation following *ipso*-nitration.

Alkyl Groups

There are many examples where modification to the alkyl side-chain occurs during electrophilic nitration reactions. The most important reactions are those in which benzyl nitrites, benzyl nitrates and arylnitromethanes are formed,[35a,37] however acetamidation,[38] acetoxylation,[39] alkoxylation,[40] arylation,[39,41] hydroxylation[42] and aldehyde, carboxylic acid and ketone formation[43] are also known.

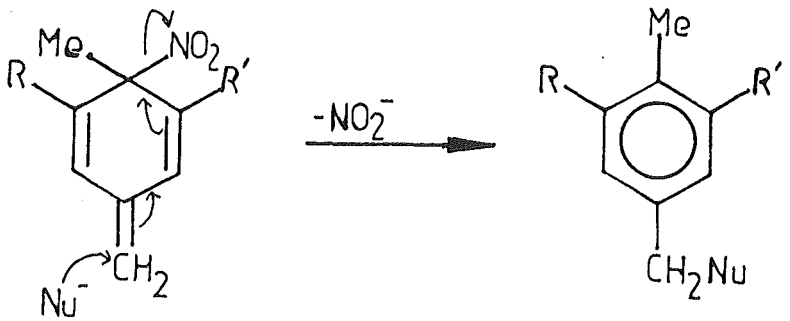
The only systematic examinations of side-chain modification have been concerned with the formation of side-chain nitro compounds. The first reported side-chain nitrations of polymethylbenzenes were effected using benzoyl nitrate.[44] Later work, by Robinson and Thompson,[45] gave, in high yield, a side-chain nitro compound from the nitration of 1,4-dimethylnaphthalene with nitric acid in acetic anhydride.



Since then there have been many nitrations of polymethyl benzenes which give side-chain nitration

products.[46] As a general rule side-chain nitration, and in fact all side-chain modification, occur at the methyl group which is *ortho* or *para* to the most activated *ipso*-position. In almost all cases the *p*-methyl group is involved. However a clear-cut exception occurs with 1-t-butyl-3,4-dimethyl- and 1-t-butyl-3,4,5-trimethyl-benzene and their derivatives. In these cases the site of *ipso*-attack is C-4, but the methyl group modified is adjacent to this.

A possible mechanism for side-chain nitration is shown in Scheme 8. Initial *ipso*-attack occurs at the most activated ring position. Subsequent loss of a proton from the methyl group *para* to the *ipso*-position gives a methylenecyclohexadiene compound, which can then be attacked by any suitable nucleophile. Attack by nitronium ion would give a side-chain nitro compound. In some substrates other side-chain substitution products such as nitrates and acetates may be formed along with side-chain nitro compounds. Given the substitution pattern in side-chain nitro formation a mechanistic pattern, shown below, is attractive.



However, the formation of a variety of other side-chain substitution products is more difficult to rationalise in

these terms, and it may be that electron transfer processes are key features in the mechanistic schemes leading to these compounds.[47a] Certainly many of these products resemble the spectrum of radical cation mediated reactions which occur during anodic[47b,c] or metal ion oxidation of aromatics.[47d]

1.3 The Nature of the Nitrating Agents

1.3.1 Concentrated Nitric Acid

Molecular nitric acid is the main species present in concentrated nitric acid, although physical measurements demonstrate the existence of significant concentrations of other species. Physical and spectroscopic studies indicate that there is appreciable self-hydration occurring according to the following scheme.[48]

$$2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

The nitration of nitrobenzene, p-chloronitrobenzene and 1-nitroanthraquinone[49] with concentrated nitric acid is according to the law, rate = k[ArH]. As nitric acid is the solvent, terms involving its concentration cannot enter the rate equation. The rate equation is consistent with reaction *via* molecular nitric acid, or any species whose concentration bears a constant ratio to the initial concentration of nitric acid. In fact the nitrating agent may account for any fraction of the total concentration of acid, provided that is is formed quickly relative to the speed of nitration.

Sulphuric acid catalyses nitration in concentrated nitric acid whereas potassium nitrate is an anticatalyst. These results are in accordance with the equilibria proposed for the self-dehydration of nitric acid. In addition, sulphuric acid allows another mode of ionisation thus further increasing the nitronium ion concentration.

$$HNO_3 + H_2SO_4 \rightleftharpoons NO_2^+ + HSO_4^- + H_2O$$

1.3.2 Nitration in Sulphuric Acid

In concentrated sulphuric acid/nitric acid reactions, the nitric acid is present predominantly as the nitronium ion. With addition of water there is a corresponding drop in the reaction rate due to the fall in concentration of nitronium ions. However, even in weakly diluted solutions nitronium ion is still spectroscopically detectable. As a general rule rate constants for nitration reach a maximum in *c.*90% H_2SO_4.[50]

1.3.3 Nitration in Acetic Acid

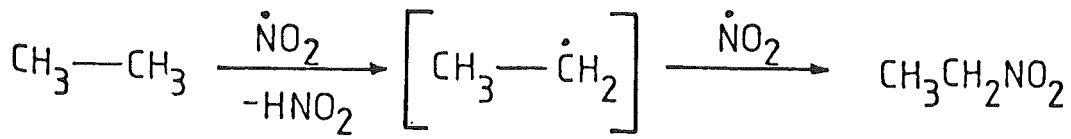
The absence of ions in mixtures of acetic acid and nitric acid is shown by their poor electrical conductivity.[51] Raman spectra of solutions of nitric acid and acetic acid only show the presence of the molecular species. Bands corresponding to nitronium and nitrate ions cannot be detected.[52]

Although nitronium ion cannot be detected, by physical methods, in solutions of nitric and acetic acids, it would seem from kinetic studies that nitronium ion is the effective nitrating agent. Nitration in acetic acid is

zeroth-order with respect to the aromatic indicating that the nitrating agent is formed from nitric acid in a slow-step Since proton transfers are unlikely to be slow, the nitrating agent is probably formed by heterolysis of protonated nitric acid to form nitronium ion. This is supported by the depression of zeroth-order reaction rates when water is added. When large concentrations of water are added to the solutions zeroth-order kinetics are no longer observed. Under these circumstances water competes successfully with the aromatic for the nitronium ions, and the zeroth-order law no longer holds.[52]

1.3.4 Nitrogen Dioxide

There is evidence in the literature that nitration of organic compounds is not confined to electrophilic attack.[53] For example free-radical nitration of aromatic compounds can be achieved by the lower oxides of nitrogen, N(III) and N(IV), and the kinetics of these reactions indicate that they involve hydrogen abstraction.[54] In the nitration of alkanes such as ethane and propane with nitrogen dioxide, in the gas phase, it has been shown that hydrogen abstraction by nitrogen dioxide is the initiating step.[55]



Nitrogen dioxide and dinitrogen tetroxide exist together in a strongly temperature-dependent equilibrium:

$$N_2O_4 \rightleftharpoons 2NO_2$$

Colourless
Diamagnetic

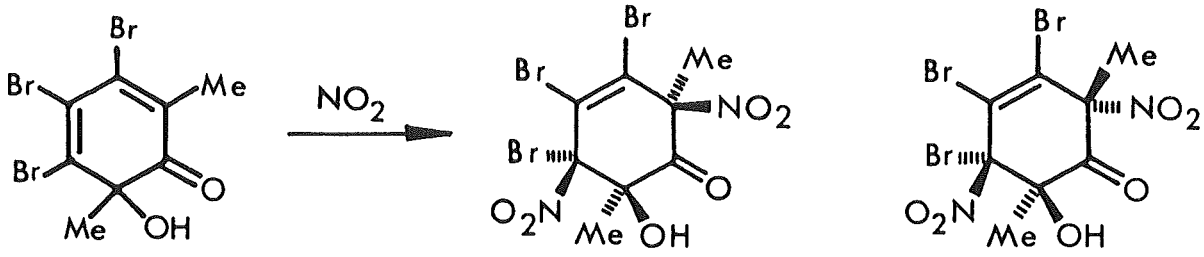
Brown
Paramagnetic

In the solid state, the oxide is wholly N_2O_4; in the liquid partial dissociation occurs and we can consider the liquid (m.p. -11.2°C) as a dilute solution of NO_2 in N_2O_4 and in the vapour at 100°C the composition is 90% NO_2, 10% N_2O_4.

Electron-spin-resonance (e.s.r.) solution studies reveal that in non-polar non-coordinating solvents, such as cyclohexane, the unpaired-electron spin-density is distributed so that 50% is located on the nitrogen atom leaving about 25% of the spin density on each oxygen atom.[56] In addition the calculated O-N-O bond angle in solution is 132-134°,[50a] not far removed from the gas phase electron diffraction values of 134°.[57] The extensive delocalisation of the unpaired-electron will oppose dimerisation.[56a]

Nitrogen dioxide also has a significant electric dipole moment of 0.316 D (1 Debye = 10^{-18} e.s.u. cm), as compared with the dipole moment of water (1.850),[58] with the nitrogen atom being the positive terminus of the dipole. This dipole moment gives the nitrogen centre of the nitrogen dioxide radical significant electrophilic character, especially toward unsaturated systems. Addition of nitrogen dioxide to unsaturated organic systems, especially carbon-carbon double bonds and aromatic nuclei, has been shown[59] to involve free-radical intermediates. The reaction of nitrogen dioxide with a conjugated dienone system[30] has been described above, in section 1.2.4. Two-step 1,4-

and 1,2-additions of nitrogen dioxide are also involved in the reaction of a number of 2,4- and 2,5-cyclohexadienones.[60]



1.4 Reaction of Phenols with Nitrogen Dioxide

Phenoxy radicals are formed by abstraction of the phenolic hydrogen atoms by nitrogen dioxide. Their presence, as intermediates, in the reactions of 2,4,6-tri-t-butylphenol[61] and 2,6-di-t-butyl-4-methylphenol[62] with nitrogen dioxide has been demonstrated by e.s.r. spectroscopy.

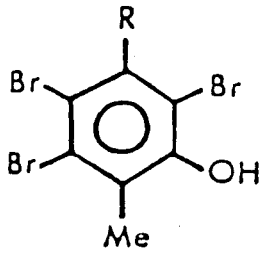
Phenoxy radicals can, in fact, be generated from their corresponding phenols by a variety of methods.[61,63] Generally, phenoxy radicals with a 2,4,6-trisubstitution pattern are more stable and those radicals with bulky 2,6-substituents which possess no α-hydrogen atoms, such as the 2,4,6-tri-t-butylphenoxy radical,[61,64] are especially stable.

E.s.r. spectroscopy measurements of phenoxy radicals[63] have been made to determine the proportion of unpaired-electron spin-density at various ring positions. As expected, the maximum electron density occurs at the C4 position, with lesser amounts at C2, C6, Cl and oxygen positions. There is

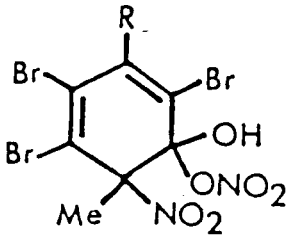
a "negative" spin density observed at C3 and C5. These results are in accord with the observed frequency of radical attack on phenoxy radicals: C4>C2,C6>C1,O>>C3,C5.

Due to extensive delocalisation, phenoxy radicals possess reasonable stability. However, in the presence of an unpaired-electron species, such as nitrogen dioxide, they can undergo rapid reaction. In the absence of an unpaired-electron species less stable, less sterically hindered phenoxy radicals can dimerise to give stable compounds.[63d]

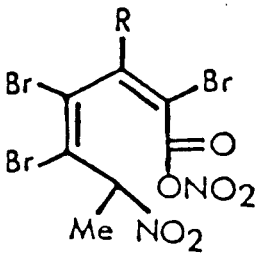
BLOCK A.



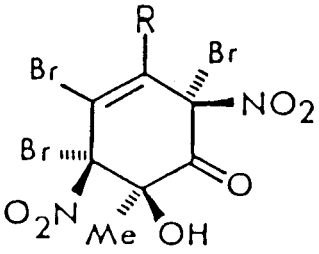
(1) R=Br
(4) R=Me



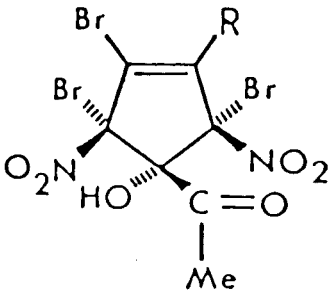
(2) R=Br
(5) R=Me



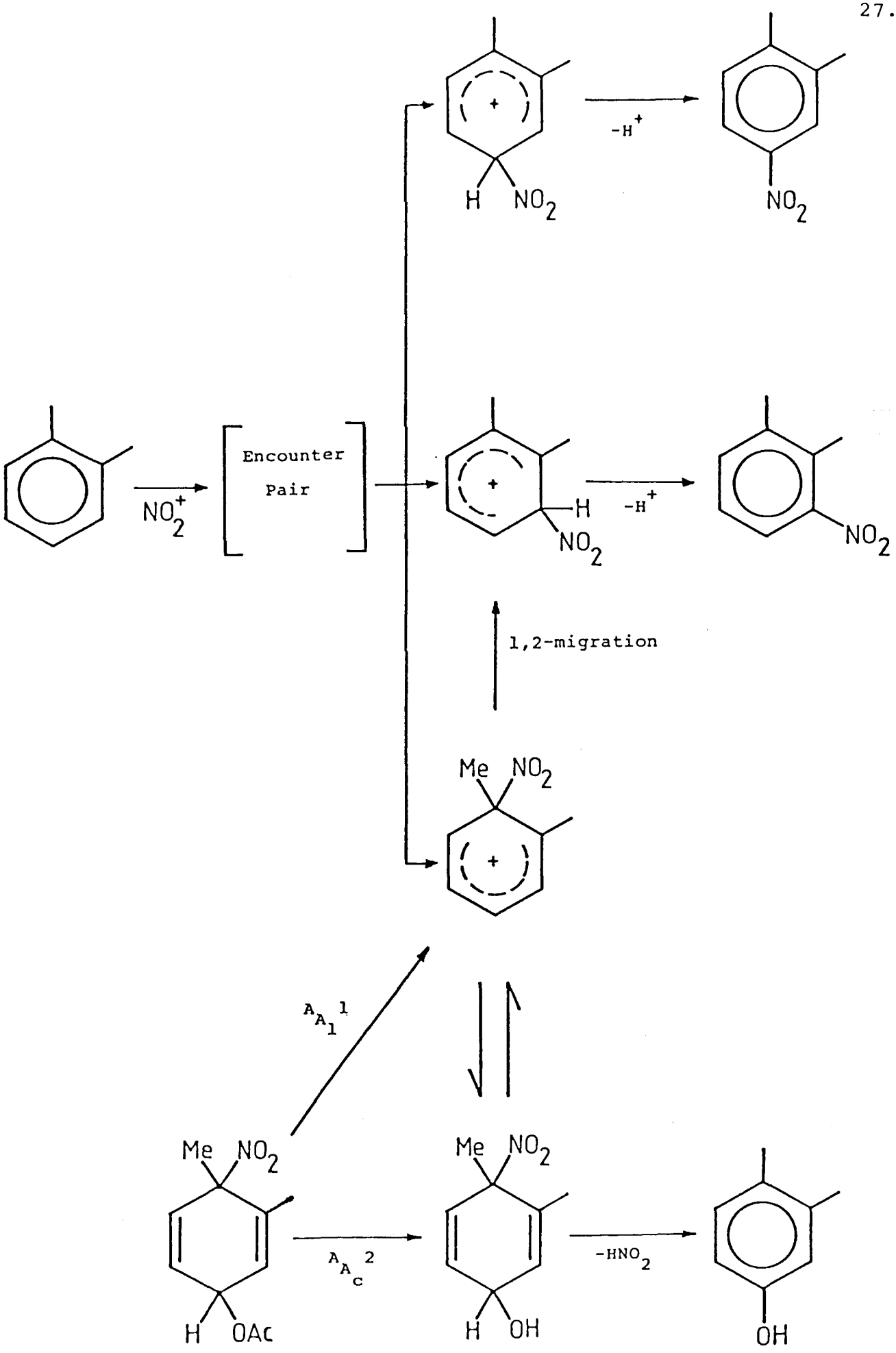
(3) R=Br
(6) R=Me



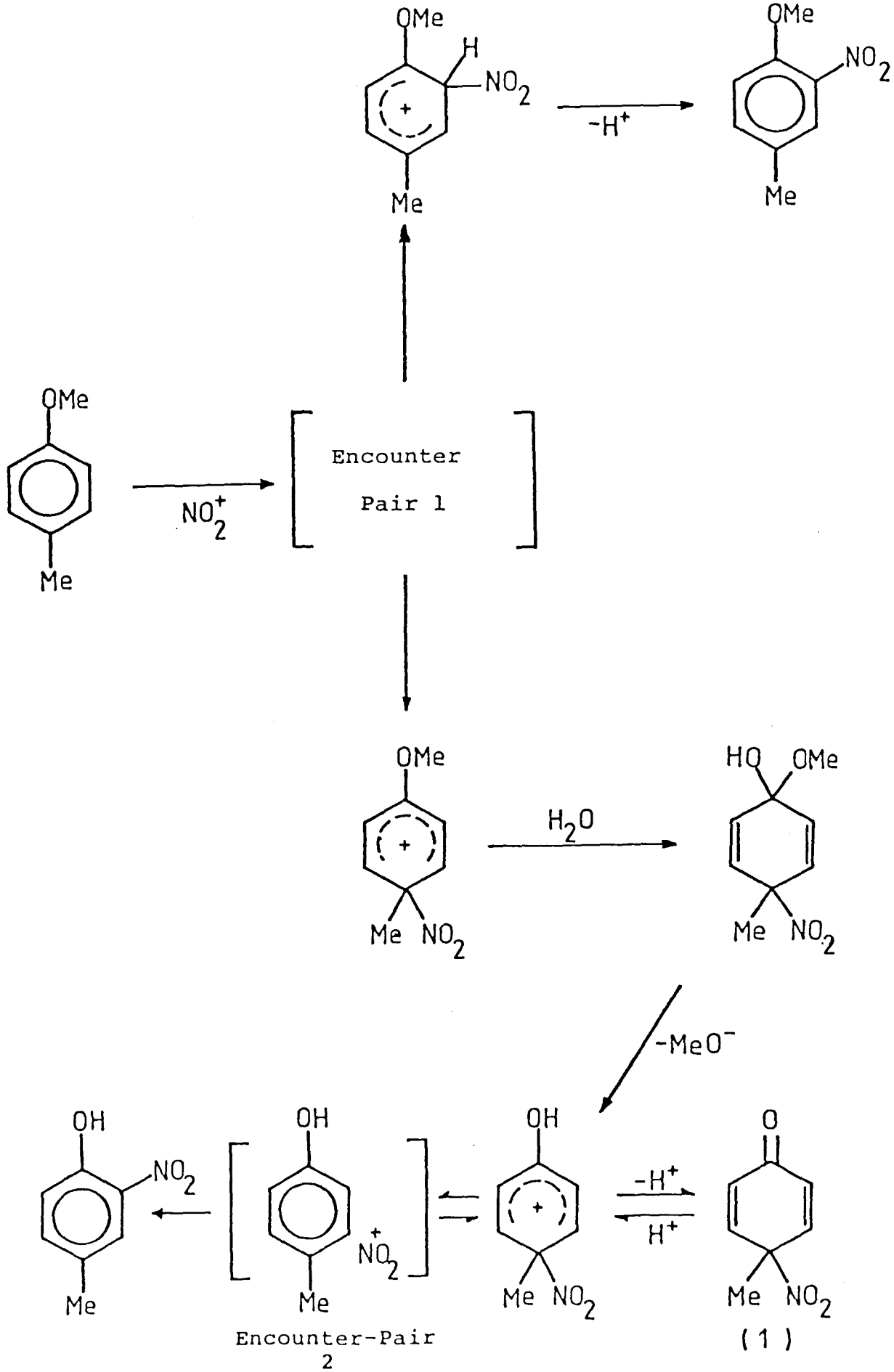
(9) R=Br
(7) R=Me



(10) R=Br
(8) R=Me



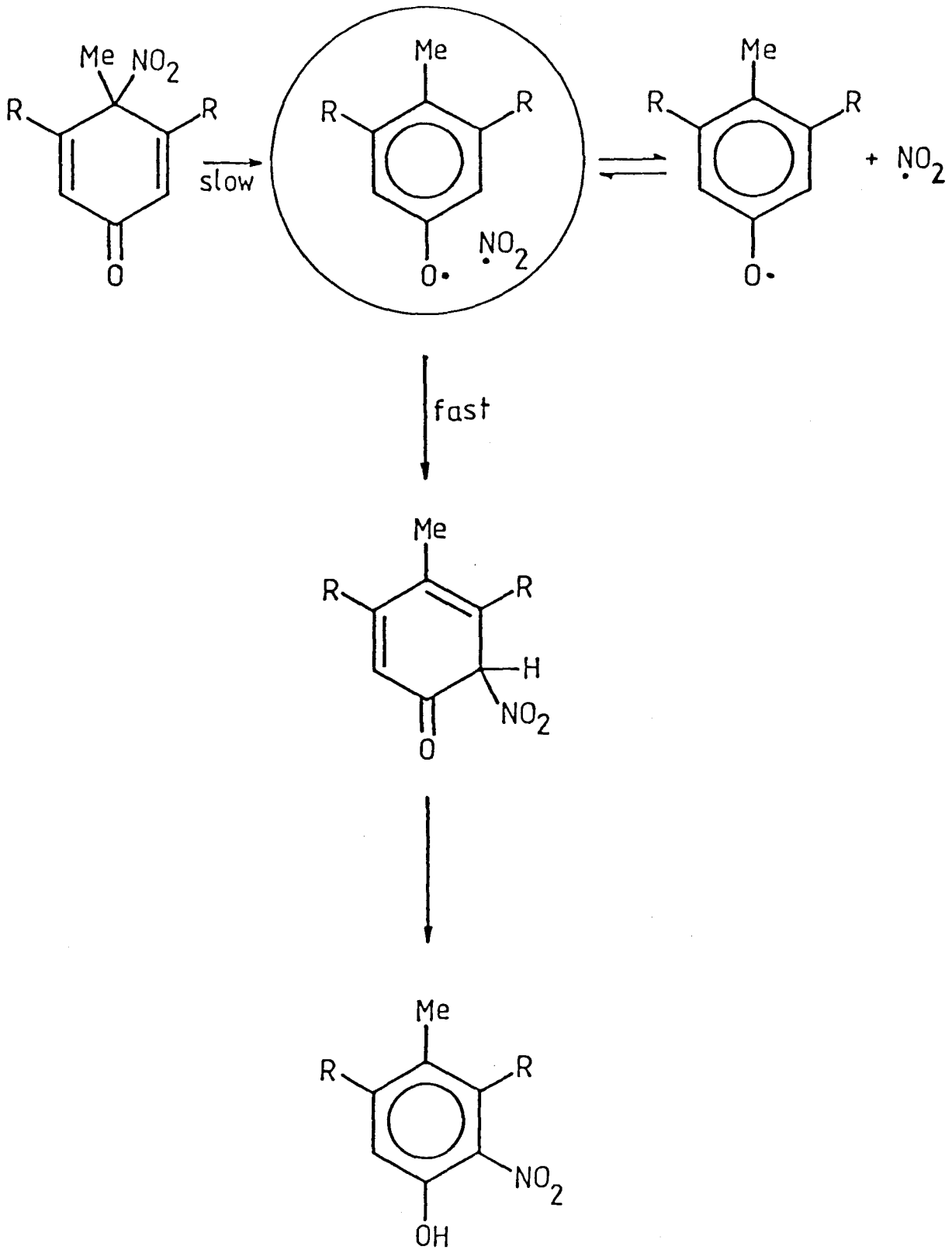
SCHEME 1.



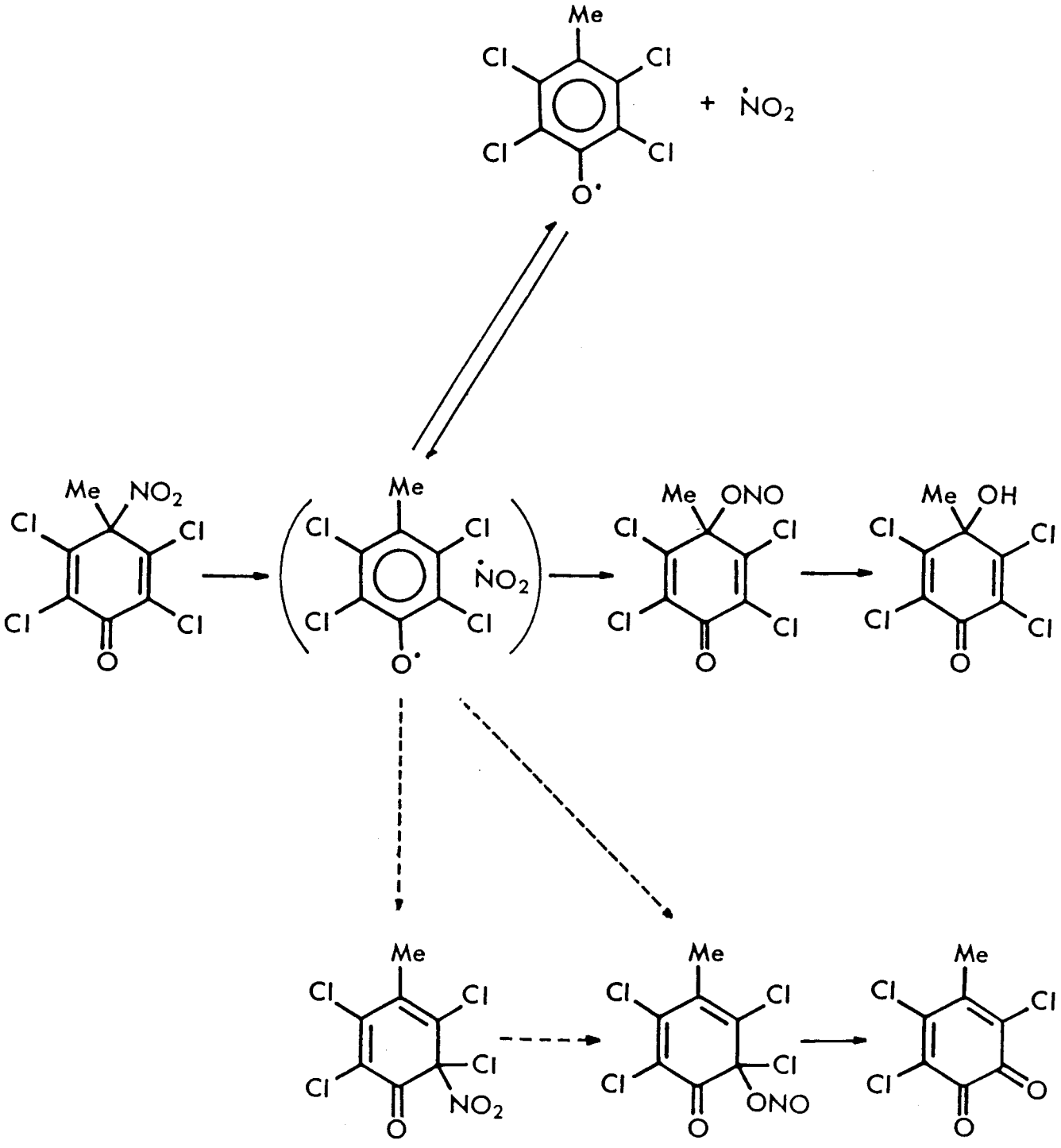
Encounter-Pair 2

(1)

SCHEME 2.


Me
NO2
R
R
O
slow
Me
R
R
O·
NO2
Me
R
R
O·
+ NO2
fast
Me
R
R
H
NO2
O
Me
R
R
NO2
OH

SCHEME 3.


Me
Cl
Cl
Cl
Cl
O·
+ ·NO2
Me NO2
Cl
Cl
Cl
Cl
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Me
Cl
Cl
·NO2
Cl
Cl
O·
Me ONO
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O
Me OH
Cl
Cl
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O
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Cl
Cl
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Cl
Cl
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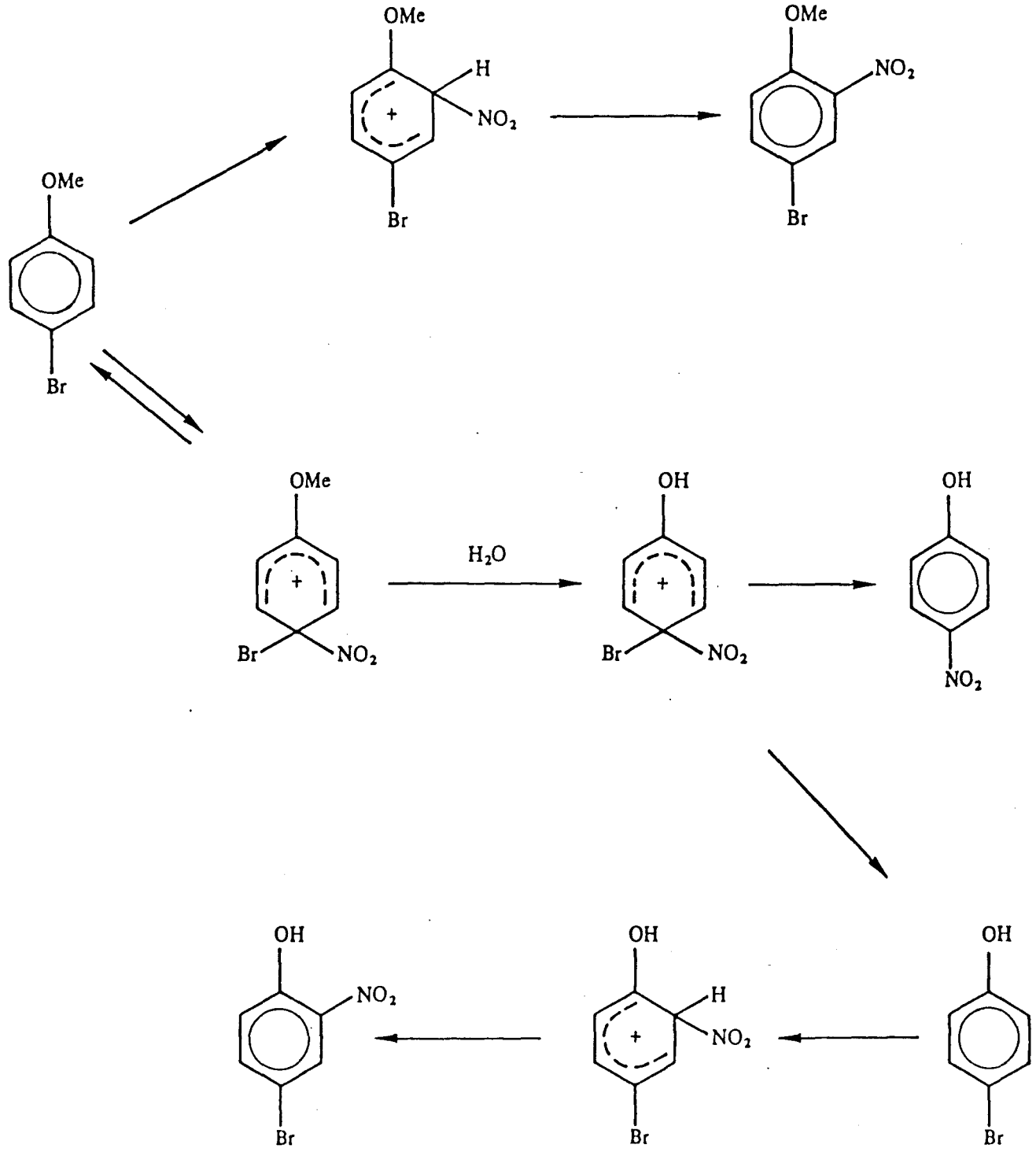
ONO
O
Me
Cl
Cl
Cl
O
O

SCHEME 4.


OMe
H
NO2
Br
OMe
NO2
Br
OMe
Br
OMe
Br
NO2
H2O
OH
Br
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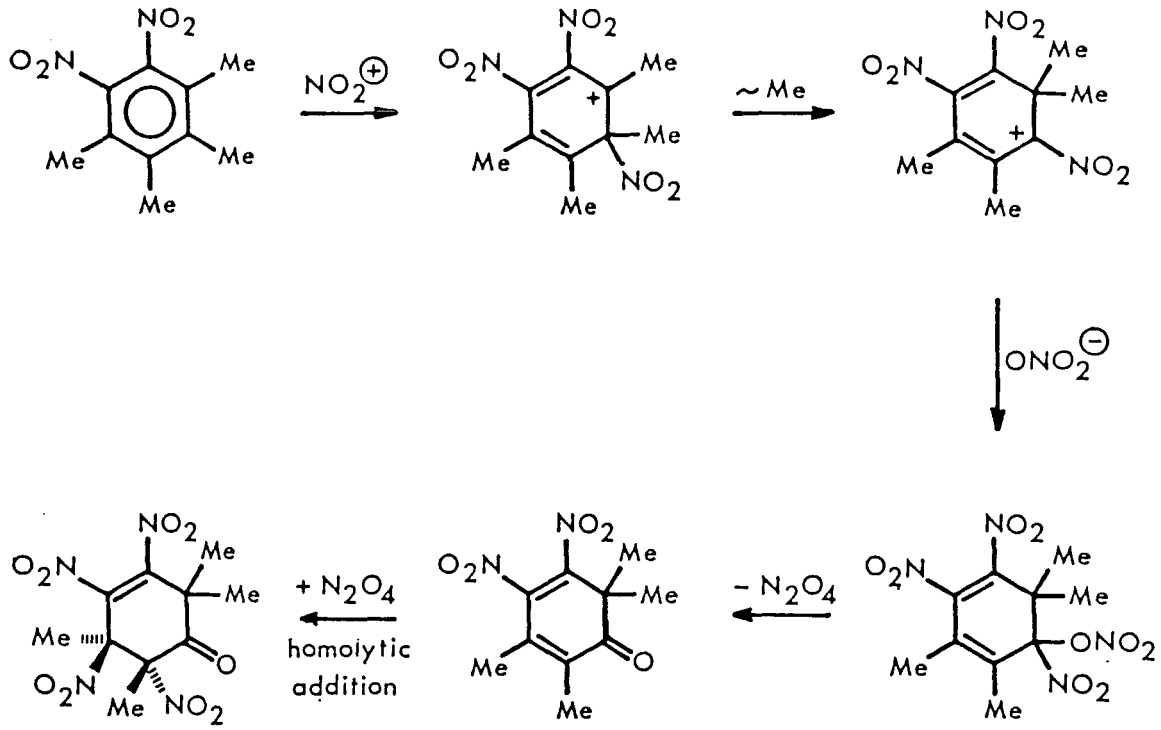
OH
NO2
OH
NO2
OH
H
NO2
Br
OH
Br
OH
NO2
Br

SCHEME 5.



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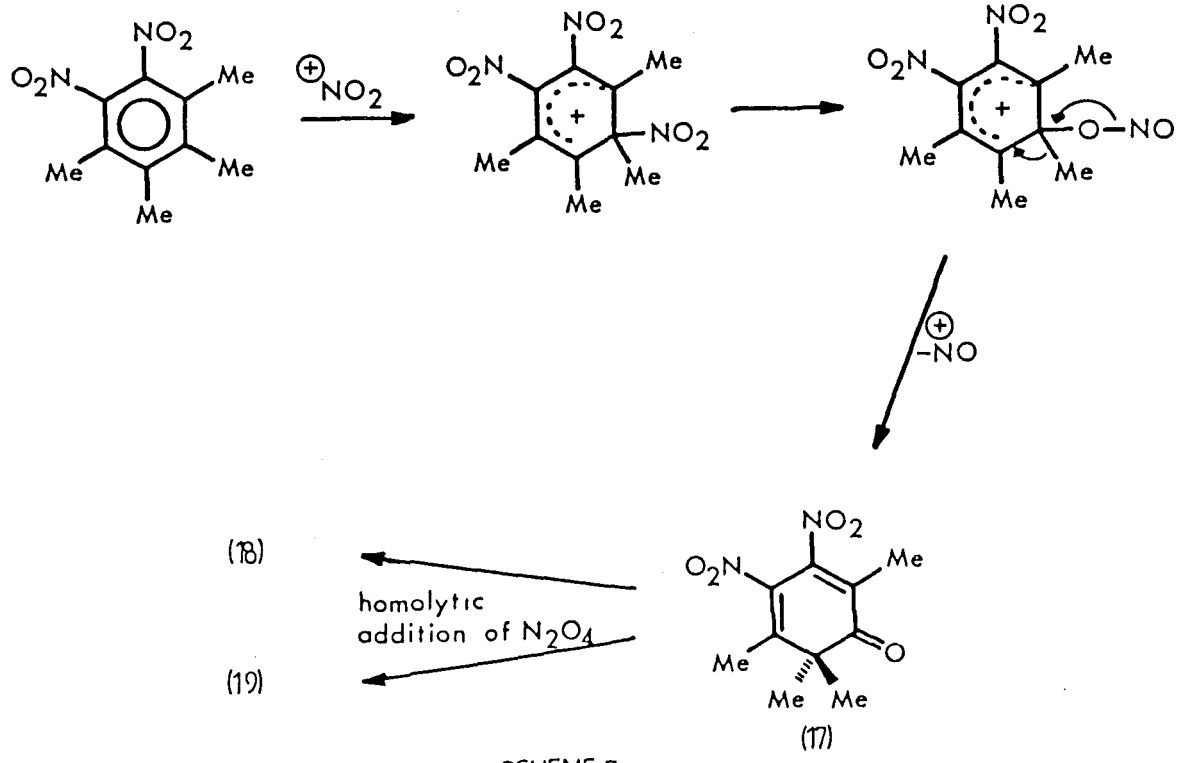
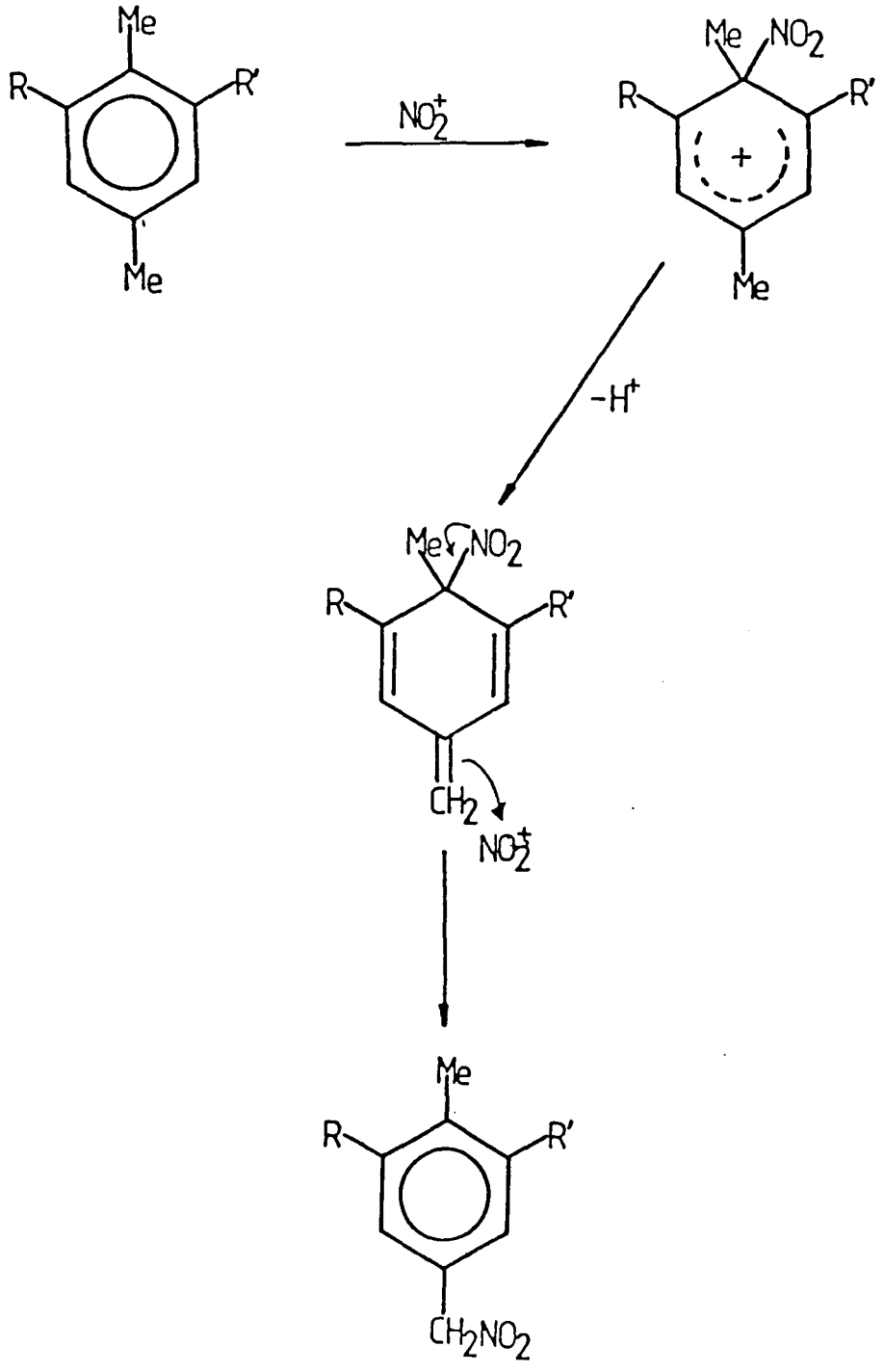


SCHEME 7.



SCHEME 8.

CHAPTER 2

NITRATION OF 4-SUBSTITUTED 2,6-DIMETHYL PHENOLS

2.1 Introduction

2.1.1 Earlier Studies of Nitrations of Polysubstituted 2-Methyl Phenols in Fuming Nitric Acid

As mentioned previously (Section 1.2.1), the nitration of 2,4,5-tribromo-3,6-dimethylphenol (4) with fuming nitric acid has been shown[10a] to give the corresponding *cis*-dinitro ketone (7); similarly 2,4-dibromo-3,6-dimethylphenol (20) gives the *cis*-dinitro ketone (21)[65] (Refer Block B).* A notable feature of these ketones, (7) and (21), is the relative all-*cis* stereochemistry of the two nitro groups and the hydroxyl group, which has been established by X-ray crystal structure analysis. Similar nitrations of 3,4,5,6-tetrabromo-2-methylphenol (1)[10b] and chlorinated 2-methyl phenols (22)[66] also yield the corresponding *cis*-nitro ketone products, (9) and (23) (Refer Block B).

In contrast to the above reactions, the nitration of 3,4,5-tribromo-2,6-dimethylphenol (24) with fuming nitric acid in acetic acid gives the pair of C2-epimeric 2,5-dinitrocyclohex-3-enones, (25) and (26),[60a] the structures of which were determined also by X-ray crystal structure analysis (Block C).

The mode of formation of these compounds is indicated in Scheme 9. A feature of this mechanism is the formation of both 4-nitro and 6-nitro dienones as intermediates. Evidence supporting this postulate is obtained from the study of 4-nitrocyclohexa-2,5,-dienone (11a) isolated by

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* Diagram Blocks and Reaction Schemes as foldouts at the end of this thesis.

crystallization from the mononitration of 3,4,6-tribromo-2,5-dimethylphenol (4). In carbon tetrachloride solution the 4-nitro dienone (11a) is shown (^{1}H n.m.r., uv.) to attain a rapid equilibrium with its 6-nitro dienone (11b)(Block C).[10a] As shown in Scheme 9, the 6-nitro dienone is subsequently converted *via* a nitro-nitrito rearrangement into the 6-hydroxy dienone, which then undergoes addition reactions with nitrogen dioxide.

2.1.2 The Mode of Formation of Nitro Dienones from Phenols in Fuming Nitric Acid

The reaction of polysubstituted phenols with nitric acid to give nitro dienones generally has been thought to proceed by initial *ipso* attack followed by loss of the hydroxyl proton (Refer Scheme 10). in 1977 Perrin suggested[67] that for nitronium ion mediated nitration of all aromatic substrates with an oxidation potential lower than that of toluene, non-bonding (outer-sphere) electron transfer processes, as shown below, should operate.

$$ArH + NO_2^+ \rightleftharpoons ArH^{\cdot+}NO_2 \rightarrow \overset{+}{A}r(H)NO_2$$

Recently calculations have been made concerning the feasibility of such electron transfer processes.[47a] These indicate that, while nitrosonium ion is an effective non-bonding electron transfer oxidant, the nitronium ion should undergo electron transfer only from extremely

oxidisable substrates. It has been postulated that observed cases of electron transfer from aromatic compounds to nitronium ion proceed *via* a mechanism involving direct bond formation to give a Wheland intermediate, followed by homolytic cleavage of the latter to give the radical cation and nitrogen dioxide:[47a] *e.g.*

$$ArH+NO_2^+ \rightleftharpoons \overset{+}{A}r\!<\!\overset{H}{N}O_2 \rightleftharpoons ArH^{\cdot+}+NO_2$$

The formation of $ArNO_2$ would then be dependent on proton loss followed by recapture of $^{\cdot}NO_2$ by $^{\cdot}Ar$.

Scheme 11 outlines how this electron transfer mechanism may be related to reactions of polysubstituted phenols with nitric acid. The formation of a Wheland intermediate followed by homolytic cleavage is common to both mechanisms. However, in reactions of polysubstituted phenols with nitric acid, proton loss would involve abstraction of the hydroxyl proton to give the phenoxy radical. Recombination of this radical with nitrogen dioxide would give the 4- or 6-nitro dienone. This mechanism is consistent with the e.s.r. spectrum, at -20°C to -110°C, of a solution of 2,6-di-t-butylphenol and pure nitric acid in nitromethane, which indicated the presence of the phenol radical cation and of the nitrogen dioxide radical.[68]

It has also been shown (Sections 1.2.4, 2.1.1) that

dienones may react in fuming nitric acid by homolytic addition of nitrogen dioxide. It would not seem unreasonable, therefore, to suggest that some dienone formation in fuming nitric acid does occur *via* nitrogen dioxide initiated hydroxyl hydrogen atom abstraction. The phenoxy radical thus formed would then react with nitrogen dioxide (Refer Scheme 12).

2.1.3 Reactions of Polysubstituted Phenols with Nitrogen Dioxide

A generalised mechanism for the reaction of polysubstituted phenols with nitrogen dioxide is given in Scheme 13. The only difference between this mechanism and the accepted mechanism (as in Scheme 9) for the reaction of polysubstituted phenols with fuming nitric acid is in the mode of formation of 4- and 6- nitro dienones. Once formed, these nitro dienones follow identical reaction pathways in both fuming nitric acid and nitrogen dioxide. Therefore a discussion of the reactions of polysubstituted phenols with nitrogen dioxide will also apply, to a large extent, to their reactions in fuming nitric acid.

(a) Formation of Nitro Dienones

Scheme 12 outlines the mode of nitro dienone formation for reactions of polysubstituted phenols with nitrogen dioxide. (See also Section 1.4). Evidence for the formation of both 4- and 6-nitro dienones is obtained from the reaction of pentamethylphenol (27) with nitrogen dioxide[69] (Scheme 14). The 4-nitro dienone (28) can be isolated directly from the product mixture. Unlike the analogous pair of compounds,(30) and (31) (Scheme 15), the 4-nitro

dienone (28) and 6-nitro dienone (29) are not interconverted under the reaction conditions. As the 4-nitro dienone (28) does not react with nitrogen dioxide the range of 4,5,6-trinitrocyclohex-2-enones and 2,5,6-trinitrocyclohex-3-enones isolated must arise from 2,5- and 4,5-addition of nitrogen dioxide to the 6-nitro dienone(29) (Scheme 14).

(b) Reactions of 4-Nitrocyclohexa-2,5-dienones with Nitrogen Dioxide

Reactions of cyclohexa-2,5-dienones with nitrogen dioxide are relatively slow, but they may occur when interconversion of a 4-nitrocyclohexa-2,5-dienone to its 6-nitrocyclohexa-2,4-dienone is not possible. The mechanism, given in Scheme 16, illustrates the various possible reaction pathways. The initially formed 4-nitro dienone (16A)* may react directly with nitrogen dioxide to give addition products, (16B) and (16C), or may rearrange to give a 4-hydroxy dienone (16D), which then undergoes addition reactions. Both cyclohexa-2,5-dienones, (16A) and (16D), are attacked by nitrogen dioxide at carbon-5 to form radical intermediates. These intermediates may then react by attack of $^{\bullet}NO_2$ at carbon-6 to form products (16B) and (16E) or by $^{\bullet}ONO$ attack, followed by hydrolysis, to give the 6-hydroxy ketones, (16C) and (16F).

For example, brief (10 min) reaction of 2,6-di-t-butyl-4-methylphenol (32) with nitrogen dioxide in cyclohexane gives essentially a quantitative yield of the 4-methyl-4-nitrocyclohexa-2,5-dienone (33).[70] Extension of the reaction time to 22h resulted in partial conversion of the initially

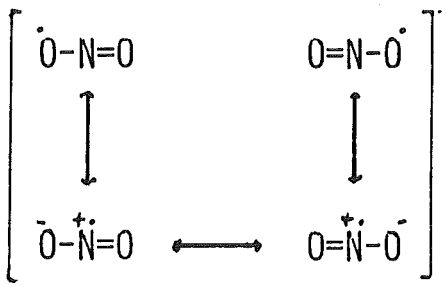
* (16A) refers to Scheme 16 compound (A) etc.

formed 4-nitro dienone (33) into a mixture of 4,5,6-trinitrocyclohex-2-enone (34) and 6-hydroxy-4,5-dinitrocyclohex-2-enone (35) (Scheme 17). Reaction of nitrogen dioxide with the 6-hydroxycyclohexa-2,4-dienone (36) (Scheme 17) does not give the 6-hydroxydinitrocyclohex-2-enone (35) proving that (35) is not formed by addition of nitrogen dioxide to the 6-hydroxy dienone (36).[70]

(c) Reactions of 6-Nitrocyclohexa-2,4-dienones with Nitrogen Dioxide

In contrast to cyclohexa-2,5-dienones, reactions of cyclohexa-2,4-dienones with nitrogen dioxide occur relatively rapidly. The reaction pathways followed are shown in Scheme 18. The 6-nitro dienone (18A) may either react directly with nitrogen dioxide to give 2,5- or 4,5- addition products, (18B), (18C) and (18D), and/or it may rearrange to give the 6-hydroxy dienone (18E), before undergoing 2,5-addition of nitrogen dioxide to give (18F) and (18G). The extent of 6-hydroxy dienone (18E) formation, relative to direct addition to the 6-nitro dienone (18A) is affected by the substituents present on the dienone structure. For example, in the reaction of pentamethylphenol[27] with nitrogen dioxide no products are formed *via* the 6-hydroxy dienone, but the compounds isolated are formed exclusively *via* additions to the 6-nitro dienone (29)[69] (Scheme 14). However, 2,3,5,6-tetramethyl-4-nitrophenol (37), which differs from pentamethylphenol only in the presence of an electron-withdrawing nitro group at carbon-4 instead of a methyl group, reacts with nitrogen dioxide through the intermediacy of both the 6-nitro and 6-hydroxy dienones, (38) and (39)[71] (Refer Scheme 19). Whereas the 2,3,4,5,6-penta-

methyl-6-nitrocyclohexa-2,4-dienone (29) (Scheme 14) reacts quantitatively with nitrogen dioxide to give addition products,[69] approximately 30% of the 2,3,5,6-tetramethyl-4,6-dinitrocyclohex-2,4-dienone (38) rearranges to give the 6-hydroxy dienone (39), which then reacts further to give 6-hydroxy-cyclohex-3-enones[71] (Scheme 19). The two processes which are competing are (i) a homolytic dissociation-recombination process leading to the formation of the 6-hydroxy dienone (39) and (ii) addition of nitrogen dioxide to the 6-nitro dienone (38). For a given C6 substituent, the rearrangement to yield the 6-hydroxy dienone (39) would be expected to be essentially unaffected by the nature of the C4-substituent. However, the rate of attack of nitrogen dioxide at C5 in the 6-nitro dienone (38) might be expected to be sensitive to the electron withdrawing or electron donating character of a C4-substituent. This is due to the substantial electrophilic character of the nitrogen centre of nitrogen dioxide illustrated by the canonical forms given below.



Any electron withdrawing substituent in the diene system would, therefore, reduce the electron availability at carbon-5 thus decreasing the rate of nitrogen dioxide addition to the 6-nitro dienone (38). Such a decrease in rate would make the nitro-nitrito rearrangement more

competitive, thereby increasing the proportion of 6-hydroxy dienone (39) formed.

An interesting feature of the addition reactions of nitrogen dioxide to 6-hydroxy dienones is the relative *cis*-stereochemistry of the C5-nitro group and the C6-hydroxy group in the cyclohex-3-enones formed. The rationalisation for this observation is outlined in Scheme 20. The stepwise conversion of the phenol (20A) into the 6-nitro dienone (20C) and thence *via* the 6-nitrito dienone (20D) into the 6-hydroxy dienone (20E) has been discussed previously. The 6-hydroxy dienone (20E) exists in a conformation determined by intramolecular carbonyl-hydroxyl hydrogen bonding. In this conformation one face of the diene system is shielded by the C6-substituent group. Attack on the diene system at carbon-5 by nitrogen dioxide can therefore only occur from the direction *cis*- to the C6-hydroxyl group. The delocalised radical intermediate (20F) thus formed is open to attack at carbon-2 by $^{\bullet}NO_2$ to form both *cis*- and *trans*-2,5-dinitro stereoisomeric products, (20G) and (20H), or by $^{\bullet}ONO$ attack, followed by hydrolysis, to give the dihydroxycyclohex-3-enone (20I) (Scheme 20).

Unlike 6-hydroxy dienones, the possible conformations of a 6-nitro dienone are not constrained by intramolecular hydrogen bonding. Initial attack on the diene system at carbon-5 can, therefore, occur either *cis*- or *trans*- to the C6- nitro group, to give delocalised radical intermediates (18F) and (18G). Further attack at carbon-2 by $^{\bullet}NO_2$ (or less commonly $^{\bullet}ONO$) would give four possible isomeric cyclohex-3-enone compounds (18C) (or (18D)). Similarly attack at carbon-4 by $^{\bullet}NO_2$ (attack at carbon-4 by $^{\bullet}ONO$ has not been

observed) would yield 4,5,6-trinitrocyclohex-2-enones (18B) (Refer Scheme 18). For example, reaction of pentamethylphenol with nitrogen dioxide gives all four possible 2,5,6-trinitrocyclohex-3-enones and three 4,5,6-trinitrocyclohex-2-enones (Scheme 14) in addition to the 2-hydroxy-5,6-dinitrocyclohex-3-enone.[69]

2.1.4 The Present Work

Nitration of pentamethylphenol (27) with nitrogen dioxide has been shown (Section 2.1.3(c)) to form trinitrocyclohex-3-enones by addition of nitrogen dioxide to the 6-nitro dienone (29) (Scheme 14).[69] In contrast 2,3,5,6-tetramethyl-4-nitrophenol (37), which differs from pentamethylphenol (27) only in the presence of an electron withdrawing nitro group at carbon-4 instead of a methyl group, reacts with nitrogen dioxide *via* both the 6-hydroxy dienone (39) and the 6-nitro dienone (38) (Scheme 19).[71] In the latter reaction addition of nitrogen dioxide to the 6-nitro dienone (38) is in competition with the conversion of the 6-nitro dienone (38) into the 6-hydroxy dienone (39). To explore further the effect of ring substituents on the partitioning of a 6-nitrocyclohexa-2,4-dienone between (i) addition of nitrogen dioxide, and (ii) rearrangement leading to the 6-hydroxycyclohexa-2,4-dienone, the reaction of 2,6-dimethyl-4-nitrophenol (40a) with nitrogen dioxide was examined. This substrate would be expected to give the 4,6-dinitrocyclohexa-2,4-dienone (45) as an intermediate. This structure (45) differs from the tetramethyl-4,6-dinitrocyclohexa-2,4-dienone (38), above, in lacking the methyl substituents at C3 and C5.

A second reason for examining the reaction of 2,6-dimethyl-4-nitrophenol (40a) with nitrogen dioxide arises from recent studies of the analogous reactions of 4-t-butyl-2,6-dimethylphenol (40b).[72] The nitration of 4-t-butyl-2,6-dimethylphenol (40b) with nitrogen dioxide in cyclohexane results in partial (*c.*30%) nitrode-t-butylation and isolation of a compound identified below as 6-hydroxy-2,4,5-trinitrocyclohex-3-enone (41).[72] The likely mode of formation of the 6-hydroxy ketone (41) seemed to be *via* reaction of nitrogen dioxide with the 2,6-dimethyl-4-nitrophenol (40a) formed as a result of nitrode-t-butylation of 4-t-butyl-2,6-dimethylphenol (40b).

As an extension to this work the nitration of 4-bromo-2,6-dimethylphenol (40c) was examined to explore the possible extent of nitrodebromination under a variety of reaction conditions.

2.2 Reaction of 2,6-Dimethyl-4-nitrophenol (40a) with Nitrogen Dioxide

The reaction of 2,6-dimethyl-4-nitrophenol (40a) with nitrogen dioxide was carried out in dichloromethane solution to ensure total solution of the phenol (40a). Removal of the solvent, under reduced pressure, gave a crude solid which was shown (^{1}H n.m.r.) to be essentially a mixture of four compounds (41) (*c.* 34%), (42) (*c.* 27%), (43) (*c.* 27%) and (44) (*c.* 10%) (Block D). Compounds (41) and (42) were isolated by fractional crystallization of the product mixture using dichloromethane/pentane solvent mixtures. The residue from fractional crystallization procedures

was further separated by h.p.l.c. methods (normal phase preparative Zorbax cyano-propyl column with hexane/ propan-2-ol as the eluting solvent) to give compounds (43) and (44).

The structures of the hydroxy trinitro ketone (42) and the dihydroxy dinitro ketone (44) were determined unambiguously by X-ray crystal structure analysis. Perspective drawings (two crystallographically independent molecules) of *t*-6-hydroxy-2,6-dimethyl-*r*-2,4,*t*-5-trinitro-cyclohex-3-enone (42), $C_8H_9N_3O_8$, m.p. 120-121°(dec.), are presented in Fig.1* with corresponding atomic coordinates in Table 1*. Corresponding information is presented for *r*-2,*t*-6-dihydroxy-2,6-dimethyl-4,*t*-5-dinitrocyclohex-3-enone (44), $C_8H_{10}N_2O_7$, m.p. 153-155°(dec.) (Fig.2, two crystallographically independent molecules, and Table 2). The spectroscopic data for compounds (42) and (44) are in accord with their established structures (see Experimental).

For compound (42) each molecule exists, in the solid state, with the alicyclic ring in a flattened skew boat conformation as can be seen from the appropriate torsional angles (Table 4). The most significant difference in conformation between the two molecules lies in the orientation of the 2-NO_2 functional group. This difference, which is evident in Fig.1, is revealed in the torsional angle C(7)-C(2)-N(2)-O(22) 31(1)° for molecule 1 and the corresponding angle for molecule 2 of 49(1)°. In both molecules the plane of the 4-NO_2 group is close to being

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* Figures as foldouts at end of Experimental Section
Tables contained in Appendix II

eclipsed with the C(4)-C(3) double bond. [torsional angle C(3)-C(4)-N(4)-O(41) 9(1)°], and the torsional angles O(1)-C(1)-C(6)-O(6) *c.* 23° and O(1)-O(6) distances *c.* 2.72Å are consistent with intramolecular hydroxyl-carbonyl hydrogen bonding in compound (42).

The two crystallographically independent molecules of the dihydroxy dinitro ketone (44) exist in similar flattened skew boat conformations (for torsional angles, Table 4). The magnitude of the differences between the two molecules are indicated by the following: (i) torsional angle C(3)-C(4)-C(5)-N(5) 87.4(5)°, molecule 1 [89.4(5)°, molecule 2], (ii) torsional angle C(3)-C(4)-N(4)-O(42) 11.4 (6)° [8.1(6)°], (iii) torsional angle H(5)-C(5)-N(5)-O(52) -2.4(4)° [-4.7(4)°], and (iv) torsional angle O(1)-C(1)-C(2)-O(2) 74.2(5)° [72.6(5)°]. As for compound (42), above, the torsional angles O(1)-C(1)-C(6)-O(6) *c.* 26° and O(1)-O(6) distances *c.* 2.68 Å are consistent with intramolecular hydroxyl-carbonyl hydrogen bonding in both molecules of compound (44). As is evident from Fig.2 and the torsion angles O(1)-C(1)-C(2)-O(2), above, intramolecular hydrogen bonding involving the 2-OH group may be excluded.

The second, less soluble, hydroxy trinitro ketone was assigned structure (41), C2-epimeric with that determined for compound (42) on the basis of spectroscopic evidence and its elemental analysis. Both structures, (41) and (42), include the *cis*-5-NO_2/6-OH stereochemistry found in all 6-hydroxy-2,5-dinitrocyclohex-3-enones formed by nitration of polysubstituted phenols with nitrogen dioxide or fuming nitric acid (Section 2.1.3(c)).[73] The spectroscopic data for compounds (41) and (42) are similar

but they do reflect the differing stereochemistry at C2.

Comparison of the ^1H n.m.r. data for a number of C2-epimeric 2,5,6-trinitrocyclohex-3-enones (Block E) reveals a correlation between the chemical shift of the C3-proton and their C2-stereochemistry. In the C2-epimers, structures (46)-(49) (Block E), for a given 5,6-dinitro stereochemistry, the H3 resonance for a *trans*-2,5-dinitro ketone occurs δ0.10-0.20 downfield of that for the corresponding *cis*-2,5-dinitro ketone (Table 5).

Table 5 'H n.m.r. ($CDCl_3$) chemical for H3 in compounds (46)-(50)

Compound	Chemical Shift (δ) for H3		
	r-2,*t*-5	*r*-2,*c*-5	Δ
(46)[60e]	6.80	6.60	0.20
(47)[60e]	6.78	6.59	0.19
(48)[72]	6.53[A]	6.40	0.13
(49)[72]	6.67[A]	6.52	0.15
(50)	8.30	8.13	0.17

[A] For CD_3CN solution

A similar comparison of the chemical shifts for the C2-epimeric 6-hydroxy-2,4,5-trinitro ketones, (41) and (42) [structure (50) in Table 5] reveals a continuation of the pattern shown in Table 5 *i.e.* that for the *trans*-2,5 dinitro compound (42) the H3 resonance occurs at δ8.30, *c.* 0.17 downfield of the H3 resonance of compound (41) (δ8.13).

The final product isolated from the reaction of the

4-nitrophenol (40a) with nitrogen dioxide was identified as the 3,4-dinitro phenol (43) on the basis of its elemental analysis and spectroscopic data.

2.3 Reaction Pathways in the Reaction of 4-Nitro Phenol (40a) with Nitrogen Dioxide

On the basis of the information obtained, above, no comment can be made about the likely mode of formation of the 3,4-dinitro phenol. However, a possible reaction mechanism is discussed later in this Chapter (Section 2.9).

By analogy with the mechanism given previously in Scheme 20 (Section 2.1.3 (c)) the three substituted cyclohex-3-enones (41), (42) and (44) may be accounted for in terms of the reaction pathways outlined in Scheme 21. Nitro-nitrito rearrangement of the initially formed 6-nitro dienone (45), followed by hydrolysis of the intermediate 6-nitrito dienone, would give the 6-hydroxy dienone (51). Reaction of the 6-hydroxy dienone (51) with nitrogen dioxide would produce the single delocalised radical intermediate (52) having *cis*-6-hydroxy-5-nitro stereochemistry. Subsequent reaction of this delocalised radical (52) with $^{\bullet}NO_2$ would yield the C2-epimeric hydroxy trinitrocyclohex-3-enones (41) and (42). Reaction of (52) with $^{\bullet}ONO$, followed by hydrolysis, would give the dihydroxycyclohex-3-enone (44).

2.4 Nitration of 2,6-Dimethyl-4-nitrophenol (40a) with Fuming Nitric Acid in Acetic Acid

Fuming nitric acid (d 1.5) was added to a stirred

suspension of the 4-nitro phenol (40a) in acetic acid and the mixture of products isolated by removal of the acids under reduced pressure. The product mixture was shown (^{1}H n.m.r.) to have a composition [(41)(*c.* 32%),(42)(*c.* 26%), (43)(*c.* 19%) and (44)(*c.*16%)], similar to that produced in the reaction of the 4-nitro phenol (40a) with nitrogen dioxide in dichloromethane. These products could be isolated by fractional crystallization and h.p.l.c. methods.

2.5 Nitration of 4-Bromo-2,6-dimethylphenol (40c) with Fuming Nitric Acid in Acetic Acid (Addition of the Phenol to the Mixed Acids)

Finely divided 4-bromo phenol (40c) was added to a stirred mixture of fuming nitric acid (d 1.5) in acetic acid. The mixture of products was obtained by removal of the acids under reduced pressure. Eight compounds were isolated by a combination of fractional crystallization from dichloromethane/pentane and by h.p.l.c. methods, but of these, compound (43), was shown subsequently to have been formed during the isolation procedure.

(a) 6-Hydroxy-2,4,5-trinitrocyclohex-3-enones (41) and (42)

Small quantities (*c.* 2% each) of the C2-epimeric hydroxy trinitro ketones (41) and (42) were isolated by fractional crystallisation using dichloromethane/pentane solvent mixtures. They were identified by comparison with authentic material, above. These compounds, (41) and (42), are thought to arise *via* nitrodebromination of the 4-bromo phenol (40a) which then undergoes nitration reactions, as reported above.

(b) 4-Bromo-6-hydroxy-2,5-dinitrocyclohex-3-enones (53) and (54)

The C2-epimeric bromo hydroxy dinitro ketones (53) and (54) (Block F) were isolated in an impure state by fractional crystallization and purified by h.p.l.c.. The structure of the more soluble isomer (54) was determined by X-ray crystal structure analysis. A perspective drawing of 4-bromo-*t*-6-hydroxy-2,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (54), $C_8H_9BrN_2O_6$, m.p. 108-109°(dec.) is presented in Fig.3 with corresponding atomic co-ordinates in Table 3. In the solid state the ring system of compound (54) exists in a flattened skew boat conformation as can be seen from the appropriate torsional angles given in Table 4. The torsional angle O(1)-C(1)-C(6)-O(6) 20.1(4)° and the O(1)-O(6) distance 2.52Å are consistent with intramolecular hydroxyl-carbonyl hydrogen bonding in compound (54).

The second, less soluble, bromo hydroxy dinitro ketone was assigned structure (53), C2-epimeric with that determined for compound (54), on the basis of its elemental analysis and by analogy with compound (54). The spectroscopic data for the two compounds, (53) and (54), are similar, but the differences between the ^1H n.m.r. resonances for H3, H5 and the 6-CH_3 for compounds (53) and (54) parallel the differences reported above for the analagous C2-epimeric hydroxy trinitro ketones (41) and (42).

(c) 4-Bromo-2,6-dimethyl-2,5,6-trinitrocyclohex-3-enone (55)

A further compound which was tentatively assigned structure (55) was obtained only in an impure state by fractional crystallization. The carbonyl stretching frequency ($\nu_{max}^{C=O}$ 1760cm^{-1}) indicates the presence of an α,α'-dinitro ketone function which is consistent with the

2,5,6-trinitrocyclohex-3-enone structure proposed. In 2,5-dinitrocyclohex-3-enones the chemical shift of the olefinic H3 in the ^1H n.m.r. spectrum is relatively insensitive to the substituent at C6[60e,72], but markedly affected by the nature of the substituent at C4. For example, examination of the ^1H n.m.r. spectrum for the analogous compounds, (56) and (57) (Block G) which differ only in the presence of a nitro group or hydroxy group at carbon-6, reveals that their H3 resonances are essentially identical i.e. (56) (δ 6.40) and (57) (δ 6.42). By comparison of the H3 chemical shifts for pairs of compounds, (41) (δ 8.13) and (53) (δ 7.08), and (42) (δ 8.30) and (54) (δ 7.23), which differ only in the nature of the C4 substituent *i.e.* 4-NO_2 or 4-Br, it is clear that compound (55) (H3, δ 7.25) has a 4-bromo substituent (Block G).

The bromo trinitro ketone (55) was unstable and decomposed on storage in both the solid state and solution. In both D_6-acetone and deuteriochloroform compound (55) was converted quantitatively into 2,6-dimethyl-3,4-dinitrophenol (43). No evidence of an intermediate, in this conversion, was detected by repeated scanning of a ^1H n.m.r. spectrum of the solution.

(d) Other Compounds Isolated

The remaining compounds isolated were 2,6-dimethyl-3,4-dinitrophenol (43), 4-bromo-2,6-dimethyl-3-nitrophenol (58) and 2,6-dimethyl-1,4-benzoquinone (59). Compounds (43) and (59) were identified by comparison with authentic material and the 4-bromo nitro phenol (58) identified from its spectroscopic data. While the bromo nitro phenol (58) and

the 1,4-benzoquinone (59) were shown to be present (^{1}H n.m.r.) in the product mixture prior to separation processes, the dinitro phenol (43) was not present initially but was formed thereafter by decomposition of the bromo trinitro ketone (55).

2.6 Nitration of 4-Bromo-2,6-dimethylphenol (40c) with Fuming Nitric Acid in Acetic Acid (Addition of Fuming Nitric Acid to the Phenol in Acetic Acid)

Addition of fuming nitric acid (d 1.5) to a solution of the bromo phenol (40c) in acetic acid, followed by removal of the acids under reduced pressure, gave a mixture of products similar to that produced on nitration of the 2,6-dimethyl-4-nitrophenol (40a), above. On the basis of the ^{1}H n.m.r. spectrum of this mixture it was estimated that nitrodebrominated products (41), (42), (43) and (44) accounted for *c.* 90% of the product mixture.

2.7 Reaction of 4-Bromo-2,6-dimethylphenol (40c) with Nitrogen Dioxide in Benzene Solution

Reaction of the bromo phenol (40c) with nitrogen dioxide in benzene also gave a mixture of products in which nitrodebrominated compounds were predominant (*c.* 80%). These products were identified by the ^{1}H n.m.r. spectrum of the mixture and comparison with the data for individual compounds, above.

2.8 Reaction Pathways in the Nitration of 4-Bromo-2,6-dimethylphenol (40c)

A notable feature of the nitration reactions of the 4-bromo phenol (40c) is the extent of nitrodebromination. Only when the phenol (40c) is added to excess fuming nitric acid in acetic acid is there significant retention of the 4-bromo substituent in the products. A possible explanation for this feature is that in the presence of excess nitric acid any nitro dienone formed would undergo further reaction before nitrodebromination could occur.

The isolation of the 4-bromo-2,5,6-trinitrocyclohex-3-enone (55) indicates that, under the reaction conditions, addition of nitrogen dioxide to the 4-bromo-6-nitrocyclohexa-2,4-dienone (60) to give the trinitro ketone (55) is competitive with the conversion of the 6-nitro dienone (60) into the 6-hydroxy dienone (61) (Scheme 22). Addition of nitrogen dioxide to the 6-hydroxy dienone (61) gives the C2-epimeric hydroxy dinitro ketones, (53) and (54), which both have the *cis*-5-NO_2/6-OH stereochemistry.

The proposed pathway for decomposition of the trinitro ketone (55) to give the dinitro phenol (43) is outlined in Scheme 22. The elimination of nitrous acid from the trinitro ketone (55), probably initiated by loss of the acidic H5, gives the 6-nitro dienone (62). Rearrangement of the 6-nitro dienone (62) would give the corresponding 4-nitro dienone (63). Proto-debromination of (63) would then yield the 3,4-dinitro-2,6-dimethylphenol (43).

The bromo nitro phenol (58) is not produced by the decomposition of the bromo trinitro ketone (55). It appears likely that this compound (58) is formed either by direct

ring nitration at C3 in 4-bromo-2,6-dimethylphenol (40c) or by an acid catalysed rearrangement of 4-bromo-2,6-dimethyl-6-nitrocyclohexa-2,4-dienone (60).

2.9 Further Comment on the Possible Mode of Formation of the 2,6-Dimethyl-3,4-dinitrophenol (43) from 2,6-Dimethyl-4-nitrophenol (40a)

The isolation of the bromo trinitro ketone (55) and its subsequent conversion into the 2,6-dimethyl-3,4-dinitrophenol (43) raises the possibility of a similar mode of formation for this dinitro phenol (43) from the nitration of 2,6-dimethyl-4-nitrophenol (40a). Such a mechanism would involve addition of nitrogen dioxide to a 6-nitro dienone (45) to form a tetranitrocyclohex-3-enone (64) (Scheme 23). Spontaneous decomposition of the postulated intermediate, by a process analogous to that for the bromo trinitro ketone (55), would yield the dinitro phenol (43).

CHAPTER 3

NITRATION OF 2,3,4,6-TETRAMETHYLPHENOL AND 1,2,3,5-TETRAMETHYLBENZENE

3.1 Introduction

In 1971 Suzuki, Sawaki and Sakimoto reported[74] the formation in small amount of the 2,3,4,6-tetraalkyl-5,6-dinitrocyclohex-3-enones (65) on nitration of 1,2,3,5-tetramethylbenzene (66a) or 2-ethyl-1,3,5-trimethylbenzene (66b) with fuming nitric acid in dichloromethane (Block H). Subsequently the ketonic products were assigned the amended structures (67) on the basis of their ^{1}H n.m.r. spectroscopic data.[75] Although the structures (67) assigned to the ketonic products are consistent with the spectroscopic data reported by Suzuki *et.al.*[74,75] it is not possible to exclude, with confidence, the alternative 2,4,6,6-tetraalkyl-2,5-dinitrocyclohex-3-enone structure (68) on the basis of the published evidence. In addition the mechanistic rationalization (Scheme 24) offered for the formation of the dinitro ketone (67a) is not compelling. Apart from the proposed methyl migration step which involves a notably unstable cationic intermediate, the final 2,3-addition of nitrogen dioxide to the cyclohexa-2,4-dienone (69) is an apparent exception to the observed pattern of 2,5- or 4,5-additions of nitrogen dioxide to cyclohex-2,4-dienone systems.[33,60e,69,73]

In view of the reservations expressed above, a reexamination of the nitration of 1,2,3,5-tetramethylbenzene with fuming nitric acid in dichloromethane was undertaken. At an early stage of this reinvestigation it became obvious

that the number and the structural variety of nitro ketones, isolable in low yield, were greater than expected. In addition to those compounds derived from nitrogen dioxide addition to the cyclohexa-2,4-dienone (69), a number of 2,4,5,6-tetramethyl-2,5,6-trinitro ketones (70) were isolated. Because of the low yield of these compounds the reaction of 2,3,4,6-tetramethylphenol[71] with nitrogen dioxide was undertaken; it was expected that this reaction would yield workable amounts of the isomeric 2,5,6-trinitro ketones (70).

3.2 Reaction of 2,3,4,6-Tetramethylphenol (71) with Nitrogen Dioxide in Benzene Solution

Reaction of the tetramethylphenol (71) with nitrogen dioxide in benzene solution gave a crude product, which was shown (^{1}H n.m.r.) to be essentially a mixture of six components. These six components (refer Block I), separated by chromatography using a Chromatotron silica gel plate and ether/petroleum ether mixtures and methanol as the eluting solvents, represented a total isolated yield of *c.*75%. A further 13 minor components accounted for the remainder of the material recovered after chromatography.

The least polar compound isolated was an unstable oil (*c.* 24%) to which the 4-hydroxy-5,6-dinitrocyclohex-2-enone (72) structure was tentatively assigned. The spectroscopic data for compound (72) are consistent with the assigned conjugated ketone structure. On storage this hydroxy dinitro ketone (72) decomposes, with loss of nitrogen dioxide, to give the 4-hydroxycyclohexa-2,5-dienone (73),

the structure of which was assigned on the basis of its elemental analysis and spectroscopic data (Block I).

The four possible stereoisomers (*d*,*l*-pairs) with the 2,5,6-trinitrocyclohex-3-enone (70) gross structure were eluted from the silica gel plate in the elution order:- (74) (*c.* 11%), (75)(*c.* 10%), (76)(*c.* 12%), (77)(*c.* 13%). Of these four compounds, only for trinitro ketone (74) were crystals obtained of a quality satisfactory for X-ray structure analysis. The structural assignments for trinitro ketones (74), (75), (76) and (77) are therefore based on (i) the X-ray structure determination for compound (74), (ii) the general similarity of the spectroscopic data for the four compounds, (iii) the order of elution of the four stereoisomers from a Chromatotron silica gel plate,[60e,69,72] (iv) their elemental analyses and (v) the correlation between C2-stereochemistry and the chemical shift of the olefinic H3.

A perspective drawing of 2,4,5,6-tetramethyl-*r*-2,*t*-5,*c*-6-trinitrocyclohex-3-enone (74), $C_{10}H_{13}N_3O_7$, m.p. 104-105° (dec.) is presented in Fig.4 with corresponding atomic co-ordinates in Table 6. In the solid state the cyclohex-3-enone ring system for ketone (74) exists in a skew boat conformation with the 5-NO_2 group in a flagpole orientation (see Table 12 for torsional angles). The planes of the 2-NO_2, 5-NO_2 and 6-NO_2 groups are orientated quite differently from each other relative to the ring carbons or geminal methyl groups; the plane of the 2-NO_2 group is close to perpendicular to the C(2)-C(7) bond, the plane of the 5-NO_2 is essentially aligned with the C(5)-C(9) bond, while the orientation of the 6-NO_2 group is indicated by the torsional angle: C(1)-C(6)- N(6)-O(61) -28.6(3)°.

Stereochemical assignments have been made, normally supported by X-ray crystal structure analysis, for the four sets of four isomeric substituted 2,5,6-trinitrocyclohex-3-enones (78),[60e] (79),[69] (80)[69] and (81)[72] (Block J). Within each set the elution order from a Chromatotron silica gel plate using ether/petroleum ether as eluents was in all cases: *r*-2,*t*-5,*c*-6-;*r*-2,*c*-5,*t*-6-;*r*-2,*t*-5,*t*-6-; *r*-2,*c*-5,*c*-6-trinitrocyclohex-3-enone. In this work the 2,5,6-trinitrocyclohex-3-enone (74) eluted first has been shown (X-ray structure analysis) to have the *r*-2,*t*-5,*c*-6-stereochemistry; the remaining trinitro ketones (75), (76) and (77) were assigned the stereochemistry appropriate to their elution order.

In addition, the correlation established in Chapter 2 between the chemical shift of a C3-proton and the C2-stereochemistry for a series of epimeric trinitrocyclohex-3-enones, supports the stereochemical assignments made for compounds (74)-(77). As shown in Table 5 (Section 2.2) for a given 5,6-dinitro stereochemistry, the H3 resonance for a *trans*-2,5-dinitro ketone occurs δ0.10-0.20 downfield of that for the corresponding *cis*-2,5-dinitro ketone. In the absence of further X-ray data, only limited stereochemical conclusions can be drawn from the ^{1}H n.m.r. data for compounds (74)-(77), *i.e.* that compound (74)(H3 δ6.47) has the *trans*-2,5-dinitro stereochemistry and that compound (77) (H3 δ6.23) has the *cis*-2,5-dinitro stereochemistry.

The remaining major product isolated from the reaction of 2,3,4,6-tetramethylphenol (71) with nitrogen dioxide was shown to have structure (82) (Block I) by X-ray crystal analysis. A perspective drawing of 2,4,5,6-tetramethyl-

r-4,*t*-5,*t*-6-trinitrocyclohex-2-enone (82), $C_{10}H_{13}N_3O_7$, m.p. 108-110° (dec.) is presented in Fig.5 with corresponding atomic coordinates in Table 7. In the solid state, the ring system of compound (82) exists in a skew-boat conformation [torsion angles: C(3)-C(2)-C(1)-C(6) 20.0(4)°; C(2)-C(3)-C(4)-C(5) -1.1(4)°]. The planes of the 5-NO_2 and 6-NO_2 groups are close to alignment with C(5)-C(9) and C(6)-C(10) bonds respectively, but the plane of the 4-NO_2 group is substantially displaced from alignment with the C(4)-C(8) bond [torsion angle: O(42)-N(4)-C(4)-C(8) -38.5(4)°]. The spectroscopic data for conjugated ketone (82) are in accord with the structure established by X-ray crystal structure analysis.

3.3 Reaction Pathways for the Reaction of 2,3,4,6-Tetramethylphenol (71) with Nitrogen Dioxide in Benzene Solution

The mode of formation of products (72), (74), (75), (76), (77) and (82) from the reaction of the tetramethyl phenol (71) with nitrogen dioxide is outlined in Scheme 25. The initial step involves formation of the 6-nitro dienone (83). Subsequent attack of $^{\bullet}NO_2$ at C5 on the 6-nitrocyclohexa-2,4-dienone (83) would give rise to a delocalised radical intermediate (84). Attack of $^{\bullet}NO_2$ at C2 of the delocalised radical intermediate (84) would give the four isomeric 2,5,6-trinitrocyclohex-3-enones (74)-(77), while $^{\bullet}NO_2$ attack at C4 would give the conjugated ketone (82). The hydroxy dinitro ketone (72) is envisaged as being formed by attack of $^{\bullet}ONO$ at C4 of the delocalised radical (84),

followed by hydrolysis. A feature of the rationalisation outlined in Scheme 25 is the implication that the 2,4,5,6-tetramethyl-6-nitrocyclohexa-2,4-dienone (83) is a key intermediate in the formation of at least 75% of the products.

3.4 Nitration of 1,2,3,5-Tetramethylbenzene (66a) with Fuming Nitric Acid

Nitration of 1,2,3,5-tetramethylbenzene (66a) with fuming nitric acid gave a complex mixture of products which were separated by a combination of column chromatography on silica gel and chromatography on a Chromatotron silica gel plate. The products isolated fall into three main categories, viz. (i) benzene derivatives which account for the bulk of the material, (ii) 6,6-dimethylcyclohexenones and (iii) 2,4,5,6-tetramethyl cyclohexenones and cyclohexa-2,5-dienones.

(i) Benzene derivatives - In addition to some unreacted 1,2,3,5-tetramethylbenzene (66a)(3%) the aromatic compounds isolated were 2,3,4,6-tetramethyl-1-nitrobenzene (85)(25%), 3,4,5-trimethylphenylnitromethane (86)(4%), 3,4,5-trimethylbenzaldehyde (87)(19%), two isomeric trimethylbenzoic acids (88)(1%) and (89)(0.3%), and the hexamethyl-9,10-anthraquinone derivative (90)(0.2%) (Block K). These compounds were identified by comparison with literature data (see Experimental Section), except for the anthraquinone derivative (90), the structure of which was assigned on the basis of its spectroscopic data and a consideration of likely cyclization mechanisms.

(ii) 6,6-Dimethylcyclohexenones - Four 6,6-dimethylcyclohexenone derivatives (91)(1%), (92)(1.3%), (93)(0.1%) and (94)(0.3%) (Block L) were isolated, and the structures of three of them [(92),(93) and (94)] were determined unambiguously by single-crystal X-ray structure determination.

A perspective drawing of 2,4,6,6-tetramethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (92), $C_{10}H_{14}N_2O_5$, m.p. 72-73° (dec.) is presented in Fig.6, (two crystallographically independent molecules with corresponding atomic coordinates in Table 8. Similar information is presented for 2,4,6,6-tetramethyl-*r*-4, *t*-5-dinitrocyclohex-3-enone (93), $C_{10}H_{14}N_2O_5$, m.p. 80-82° (dec.) (Fig.7; two crystallographically independent molecules, and Table 9) and for *r*-2-hydroxy-2,4,6,6-tetramethyl-*t*-5-nitrocyclohex-3-enone (94), $C_{10}H_{15}NO_4$, m.p. 131-132° (dec.) (Fig.8 and Table 10). For each of the compounds (92) and (93) the structure contains two, well separated, crystallographically independent molecules.

Superposition of the two independent molecules of compound (92) revealed that the differences were minor, with the most significant difference being the orientation of the plane of the 5-NO_2 group relative to the geminal H(5) [torsion angles: O(52)-N(5)-C(5)-H(5) 10.5(3)°; O(151)-N(15)-C(15)-H(15) 6.5(2)°]. For compound (92) both molecules exist, in the solid state, in a skew boat conformation, with the plane of the 5-NO_2 group aligned with the geminal C-H bond and in the flagpole orientation (for torsional angles refer Table 12).

Superposition of the two independent molecules of compound (93) reveal that the minor differences observed were a consequence of differences in the flattened half-chair

ring conformations of the two molecules [torsion angles: molecule 1, C(3)-C(2)-C(1)-C(6) 11(1)°, C(2)-C(3)-C(4)-C(5) 8(1)°; molecule 2, C(13)-C(12)-C(11)-C(16) 8(1)°, C(12)-C(13)-C(14)-C(15) 1(1)°]. The plane of the 5-NO_2 group is aligned with the geminal C-H bond whereas the plane of the 4-NO_2 is nearly aligned with the C(3)-C(4) bond (in both molecules).

In compound (94) the ring exists in a skew-boat conformation in the solid state with the 5-NO_2 group in the flagpole orientation (refer Table 12). As for compounds (92) and (93) the plane of the 5-NO_2 group is aligned with the C(5)-H(5) bond. The absence of intramolecular hydroxyl-carbonyl hydrogen bonding, in compound (94), is indicated by the O(1)-O(2) bond distance of 3.12 Å.

The structure of compound (91), the dinitro ketone reported earlier by Suzuki *et.al.*,[74,75] is the C2-epimer of compound (92), the structure of which has been determined, above. Comparison of the spectroscopic data for the pair of compounds (91) and (92) reveals marked similarities and only one significant difference, *i.e.* in the chemical shift of the olefinic H3. As has been demonstrated previously (Sections 2.2,3.2), this difference is a function of C2-stereochemistry, the H3 resonance occurring downfield by δ0.10-0.20 for *r*-2,*t*-5-dinitrocyclohex-3-enones [e.g. (92) (δ6.25)] as compared with the values for their C2-epimeric *r*-2,*c*-5-dinitrocyclohex-3-enones [e.g. (91)(δ6.08)]. As the structure of compound (92) is known, the dinitro ketone reported by Suzuki *et.al.*[74,75] is assigned structure (91).

(iii) 2,4,5,6-Tetramethyl-cyclohexenones and -cyclohexa-2,5-dienones - The remaining six compounds isolated from the fuming nitric acid nitration of 1,2,3,5-tetramethylbenzene (66a)

were the two 4-hydroxycyclohexa-2,5-dienones (73)(0.3%) and (95)(0.3%), the 6-hydroxy-2,5-dinitrocyclohex-3-enone (96) (0.05%) and three stereoisomeric 2,5,6-trinitrocyclohex-3-enones (74)(0.6%), (75)(0.4%) and (76(1%) (Block M). Compounds (73), (74), (75) and (76) were identified by comparison with authentic samples, and the structure of compound (95) was indicated by its spectroscopic data which was consistent with the assigned 4-hydroxy cross conjugated dienone structure.

The structure of the hydroxy dinitro ketone (96) was determined by X-ray crystal structure analysis. A perspective drawing of *c*-6-hydroxy-2,4,5,6-tetramethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (96), $C_{10}H_{14}N_2O_6$, m.p. 80-82° (dec.), is presented in Fig.9 with corresponding atomic coordinates in Table 11. In the solid state the ring system of compound (96) exists in a flattened half-chair conformation with the 5-NO_2 group pseudoaxial (Table 12). The torsion angle: O(1)-C(1)-C(6)-O(6) 13.8(4)°, and the O(1)-O(6) distance 2.12 Å are consistent with intramolecular hydroxyl-carbonyl hydrogen bonding in compound (96).

3.5 Reaction Pathways in the Fuming Nitric Acid Nitration of 1,2,3,5-Tetramethylbenzene (66a)

Comment on the reaction pathways operating in the nitration of 1,2,3,5-tetramethylbenzene (66a) with fuming nitric acid must be limited because of the low accountability of material from the reaction [<60% including recovered (66a) (*c.* 3%)]. The major reaction pathways were conventional ring nitration (*c.* 24%) and side-chain modification.

It appears that side-chain modification proceeds largely *via* the *ipso* Wheland intermediate (97) formed by nitronium ion attack on the tetramethyl benzene (66a) at carbon-2. It also appears likely that this *ipso* Wheland intermediate (97) is involved in the formation of the 6,6-dimethylcyclohexenone products (91), (92), (93) and (94). The reaction mechanism for this process (Scheme 26) is analagous to that for the formation of 2,5,6,6-tetramethyl-2,3,4,5-tetranitrocyclohex-3-enones (18) and (19) (Block M) on reaction of 1,2,3,4-tetramethyl-5,6-dinitrobenzene with fuming nitric acid, discussed previously (Section 1.2.4).

Compounds (73), (74), (75), (76) and (96) are envisaged as arising *via* the Wheland intermediate (98) formed by *ipso* attack at carbon-1 (refer Scheme 27). Capture of this *ipso* Wheland intermediate (98) by a suitable nucleophile *e.g.* H_2O, $^-NO_3$ followed by elimination of nitrous acid would give compound (99). The 6-nitro dienone formed *via* compound (99) would then undergo analogous reactions to those outlined in Scheme 25. The proposed mechanism is given in Scheme 27.

CHAPTER 4

NITRATIONS OF SOME SUBSTITUTED 1,2,3-TRIMETHYL BENZENES AND 1,2,4,5-TETRAMETHYL-3,6-DINITROBENZENE

4.1 Introduction

In 1972 Suzuki and Nakamura[76] reported the nitration of 1,2,3,5-tetramethyl-4,6-dinitrobenzene (100) with fuming nitric acid to give the side-chain modified products (101a), (101b), (101c) and (101d) (Block N).

The initial step in the formation of these products is probably nitronium ion attack at the most activated C2 position to give the *ipso* Wheland intermediate (102). In view of these results, an examination of the nitration of 1,2,3-trimethyl-4,6-dinitrobenzene (103) was undertaken. For this substrate, initial reaction would also involve nitronium ion attack at the C2 position to form the *ipso* Wheland intermediate (104), analogous to (102), but lacking the C5-methyl group of (102). Reaction possibilities involving the 5-methyl group are therefore denied to it, but the unsubstituted 5-carbon of compound (103) does allow other reaction possibilities.

The nitrations of 1-bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105) and of 1,2,3-trimethyl-4,5,6-trinitrobenzene (106), with fuming nitric acid, were also examined to investigate (i) the effect of electron withdrawing ring substituents and (ii) the presence of a non-modifiable nitro group at carbon-5.

4.2 Mixed Acid Nitration of 1,2,3-Trimethylbenzene - Preparation of 1,2,3-Trimethyl-4,6-dinitrobenzene (103)

1,2,3-Trimethylbenzene was nitrated with fuming nitric acid (d 1.5) in concentrated sulphuric acid (d 1.84).[77] The crude product isolated was separated by column chromatography to give the required 1,2,3-trimethyl-4,6-dinitrobenzene (103) (61%) as the major product. In addition to compound (103) and the expected[77] minor product 1,2,3-trimethyl-4,5-dinitrobenzene (107)(14%), a significant amount of the fully substituted trimethyl trinitro compound (106)(16%) was obtained (Block N). Further investigation revealed that the trinitro compound (106) was the product of further nitration of 1,2,3-trimethyl-4,5-dinitrobenzene (107); the isomeric 1,2,3-trimethyl-4,6-dinitrobenzene (103) was unreactive under these reaction conditions.

4.3 Nitration of 1,2,3-Trimethyl-4,6-dinitrobenzene (103) with Fuming Nitric Acid

Nitration of the dinitro compound (103) with fuming nitric acid at 20° for 18 weeks, followed by removal of the nitric acid under reduced pressure, gave a residue, part of which was only sparingly soluble in dichloromethane. Fractional crystallization of this insoluble material, from ether/pentane mixtures, gave oxalic acid dihydrate and dimethylpropanedioic acid (108). The oxalic acid dihydrate was identified from its m.p. and comparison of its infrared spectrum with that for authentic material. The dimethylpropanedioic acid (108) was identified from its spectroscopic data.

The dichloromethane soluble fraction was separated into

its components by fractional crystallization from ether/pentane mixtures and yielded 2,6-dimethyl-3,5-dinitrobenzoic acid (109), the 4-hydroxy dienone (11)(110) and unreacted dinitro compound (103). The structural assignment for the substituted benzoic acid (109) was made on the basis of its elemental analysis and spectroscopic data. The ^{1}H n.m.r. spectrum indicated the presence of two equivalent methyls (δ 2.52) and one aromatic proton (δ 8.50). The 4-hydroxy dienone (110) is a known compound[78] and its identification is supported by its spectroscopic data.

The yields of the significant products, above, were dimethylpropanedioic acid (108)(72%), substituted benzoic acid (109)(9%) and 4-hydroxy dienone (110)(8%). Two of these products, (108) and (110), are envisaged as being formed *via* the *ipso* Wheland intermediate (104) (Scheme 28). Nitro-nitrito rearrangement of the Wheland intermediate (104) would give the nitrito cation (111), which may rearrange, with loss of ^{+}NO, to give the 6,6-dimethylcyclohexa-2,4-dienone (112). This reaction sequence is analogous to those outlined previously (Sections 1.2.4,3.5) for the formation of the tetranitro ketones (15) and (68a) on nitration of 1,2,3,4-tetramethyl-5,6-dinitrobenzene and 1,2,3,5-tetramethylbenzene (66a). Oxidation of the 6,6-dimethylcyclohexa-2,4-dienone (112) would be expected to give dimethylpropanedioic acid (108).

Formation of the 4-hydroxy dienone (110) from the *ipso* Wheland intermediate (104) involves attack by water or nitrate ion to give the diene (113). Oxidation or loss of nitrous acid from the diene (113) would then give the 4-nitro dienone (114). Conversion of this 4-nitro dienone (114) into the 4-hydroxy dienone (110) may occur during the nitration reaction

or subsequently during the isolation procedure.

4.4 Mixed Acid Nitration of 1-Bromo-2,3,4-trimethylbenzene - Preparation of 1-Bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105)

Nitration of 1-bromo-2,3,4-trimethylbenzene with fuming nitric acid in sulphuric acid[79] gave a crude product which was separated by column chromatography using 5% deactivated alumina. In addition to the expected[79] 1-bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105)(75%) the two possible mononitro products, (115)(12%) and (116)(10%) (Block O), were isolated.

4.5 Nitrations of 1,2,3-Trimethyl-4,5,6-trinitrobenzene (106) and 1-Bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105)

Long term (18 weeks) storage of 1,2,3-trimethyl-4,5,6-trinitrobenzene (106) in fuming nitric acid at 20° revealed that compound (106) was unreactive towards fuming nitric acid. Similarly, 1-bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105) did not undergo reactions with fuming nitric acid. These results indicate that the effect of an extra electron-withdrawing bromo or nitro group is sufficiently deactivating to prevent electrophilic attack.

4.6 Nitration of 1,2,4,5-Tetramethyl-3,6-dinitrobenzene (117) with Fuming NItric Acid

On nitration of the dinitro compound (117) with fuming nitric acid (d 1.5) at 20° for 22 weeks, a colourless solid

separated from solution. This solid was shown (^{1}H n.m.r.) to be a mixture (1:7) of unreacted dinitro compound (117) and the substituted benzoic acid (118). The second compound (118), isolated by fractional crystallization, was identified by its elemental analysis and spectroscopic data. The ^{1}H n.m.r. spectrum for compound (118) indicated the presence of three methyl groups [two equivalent (δ 2.36) and one other (δ 2.28)].

The nitric acid was removed from the filtrate, under reduced pressure, to give a solid residue. Fractional crystallization of this residue from dichloromethane gave dimethylpropanedioic acid (108) and a second compound identified as the nitro dicarboxylic acid (119) (Block O) from its elemental analysis (consistent with molecular formula $C_8H_{11}NO_6$) and spectroscopic data. The functional groups present in the dicarboxylic acid (119) were indicated by its infrared spectrum, and the ultraviolet spectrum, [λ_{max} 242 nm (ε 2000)], is consistent with the presence of a conjugated carboxylic acid function in its structure. The ^{1}H n.m.r. spectra for compound (119) indicates the presence of three methyl groups (two equivalent and one other) and the ^{13}C n.m.r. resonances are appropriate for the assigned structure [C4, δ 46.1; C2, δ 124.9; C1 and C5, δ 174.2 and 176.9; a resonance for C3 was not observed]. The stereochemistry of the alkene function could not be determined from the spectroscopic data and its determination, by X-ray crystal analysis, was impossible because of extensive twinning in the crystalline state. The stereochemical assignment, therefore, was made on the basis of a consideration of the possible mode of formation of compound (119), see below.

The residues from the above fractional crystallizations

were combined and the resulting mixture separated by chromatography using a Chromatotron silica gel plate and ether/petroleum ether mixtures as the eluting solvent. This separation gave further unreacted dinitro compound (117), substituted benzoic acid (118), and the nitro dicarboxylic acid (119). The overall yields of products were substituted benzoic acid (118)(49%), nitro dicarboxylic acid (119)(33%) and dimethylpropanedioic acid (108)(11%).

Two of the products, (108) and (119), are envisaged as being formed *via* the *ipso* Wheland intermediate (120) (Scheme 29). The conversion of this intermediate (120) into the 6,6-dimethylcyclohexa-2,4-dienone (121) is analogous to that shown in Scheme 28 and to that reported earlier[33] (Sections 1.2.4,3.5). Oxidation of the 6,6-dimethylcyclohexa-2,4-dienone (121) by fuming nitric acid might be expected to yield the dimethylpropanedioic acid (108) and the nitro dicarboxylic acid (119) with the (E)-configuration.

CHAPTER 5

EXPERIMENTAL METHODS

5.1 Apparatus, Materials and Instrumentation

Infrared spectra were recorded on a Shimadzu IR-27G spectrophotometer for liquid films and nujol mulls. Ultraviolet absorption spectra were determined for chloroform solutions on a Varian DMS 100 spectrophotometer.

Routine ^{1}H n.m.r. spectra were obtained for carbon tetrachloride, deuteriochloroform, deuterioacetonitrile, deuterioacetone and deuteriodimethyl sulphoxide solutions, with tetramethylsilane as an internal reference. N.M.R. spectral parameters were derived by first-order analysis and, wherever required and possible, confirmed by double irradiation experiments. All chemical shifts are expressed as parts per million (ppm) downfield from TMS and are quoted as position (δ), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), relative integral and coupling constants (J,Hz).

Microanalyses were carried out by Professor A.D. Campbell and associates, University of Otago.

Melting points were determined in open capillaries and are uncorrected.

Preparative scale column chromatography was carried out using Laporte Grade H alumina (100-300 mesh), deactivated by the addition of 5%v/v of 10% aqueous acetic acid, or silica gel (Grade 923). In addition, preparative scale chromatography was routinely carried out utilising a Chromatotron (a preparative, centrifugally accelerated,

radial, thin-layer chromatograph. Model 7924, Harrison Research Inc.) equipped with rotors coated with Silica gel PF-254 (with $CaSO_4.\frac{1}{2}H_2O$ type 60 for TLC, Merck: E.M. Laboratories Incorporated, item number 7749) of various thicknesses (generally 2mm).

High performance liquid chromatography (h.p.l.c.) was performed on a Varian 5000 Liquid Chromatograph using a Rheodyne 7125 injector, a Varian UV-50 ultraviolet-visible variable wavelength detector and a Hewlett Packard 3390A integrating recorder or a Waters 400 differential refractometer. Semipreparative and analytical normal phase chromatography were achieved on a Dupont Zorbax cyanopropyl column (9.4 mm I.D. x 25 cm) and a Brownlee Labs. Diol OH-10A analytical column (4.6 mm I.D. x 25 cm). Preparative normal phase chromatography was routinely undertaken using a Merck Lobar® cyano-propyl column (25 mm I.D. x 31 cm). The solvents employed for normal phase separations were hexane/propan-2-ol which were either Waters Chromatographic quality or carefully purified and dried prior to use.

All solvents used were either of analytical grade (AR) or were purified and dried according to standard procedures.[80] "Ether" refers to commercial diethyl ether distilled off sodium hydride, and "Petroleum ether" refers to petroleum ether (50-70°C) distilled off phosphorous pentoxide.

The nitrogen dioxide used, was prepared by the method described by Kevin Sutton (Ph.D. thesis: University of Canterbury).

5.2 Experimental Relating to Chapter 2

2,6-Dimethyl-4-nitrophenol[81]

To a stirred solution of 2,6-dimethylphenol (1g) in acetic acid (5ml), was added 5ml of a solution made up as follows: water (1ml), acetic acid (20ml) and fuming nitric acid (d 1.5; 3ml). The reaction mixture was poured into excess water, and sodium carbonate solution added until the solution was distinctly alkaline. It was then filtered to remove the 3,3',5,5'-tetramethyldiphenoquinone (0.4g), m.p. 187-188° [lit.[82] 184-185°], ν_{max} (Nujol) 1630, 1590 cm^{-1}, extended quinone.

The filtrate was acidified, the 2,6-dimethyl-4-nitrophenol (40a) (0.5g) collected by filtration and then recrystallized from carbon tetrachloride to give material, m.p. 172-173° [lit.[81] 170-171.5°]. ν_{max} (Nujol) 3400, OH; 1590, aromatic; 1515, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.33, 6H, methyls; 7.93, 2H, H3/H5.

Reaction of 2,6-Dimethyl-4-nitrophenol (40a) with Nitrogen Dioxide in Dichloromethane

A solution of the phenol (40a)(1g) in dichloromethane (10ml) was deoxygenated by a stream of pure nitrogen. The solution was cooled to 0° and nitrogen dioxide was bubbled through the stirred solution for 30s. The resulting mixture was stirred under an atmosphere of nitrogen dioxide at 20° for 2h. The excess nitrogen dioxide was then removed in a stream of nitrogen, and the solvent removed under reduced pressure to give a solid residue (*c.* 1.57g). The residue was shown (^1H n.m.r.) to be essentially a mixture of four compounds (41)(34%), (42)(27%), (43)(27%)

and (44)(10%); each of these compounds was isolated and characterised, below.

Fractional crystallization of the residue, above, from dichloromethane/pentane mixtures gave pure samples of two compounds:

(i) *c*-6-Hydroxy-2,6-dimethyl-*r*-2,4,*c*-5-trinitrocyclohex-3-enone (41), m.p. 131-131.5° (dec.). (Found: C, 34.9; H, 3.5; N, 15.0. $C_8H_9N_3O_8$ requires C, 34.9; H, 3.3; N, 15.3%). ν_{max} (Nujol) 3500, OH; 1750, C=O; 1680, C=C; 1590, 1573, 1558, 1320 cm^{-1}, NO_2. ^1H n.m.r. (CD_3COCD_3) δ 1.78, s, C6-Me; 2.18, s, C2-Me; 6.33, S, H5; 8.13, s, H3. ^{13}C n.m.r. (CD_3COCD_3) δ 24.1; 77.8; 89.6; 90.2; 136.9; 145.0, 196.0.

(ii) *t*-6-Hydroxy-2,6-dimethyl-*r*-2,4,*t*-5-trinitrocyclohex-3-enone (42), m.p. 120-121° (dec.). ν_{max} (Nujol) 3525, OH; 1750, C=O; 1680, C=C; 1590, 1570, 1552, 1320 cm^{-1}, NO_2. ^1H n.m.r. (CD_3COCD_3) δ 1.67, S, C6-Me; 2.23, s, C2-Me; 6.37, s, H5; 8.30, s, H3. ^{13}C n.m.r. (CD_3COCD_3) δ 24.2, 24.3, 74.6, 89.4, 90.3, 146.0, 196.2. Structure determined by X-ray crystal structure analysis (see Appendix II).

The residues from the above fractional crystallizations were combined and two further components were isolated from this mixture by h.p.l.c. on a preparative Zorbax-cyanopropyl column using hexane/propan-2-ol (7:3) as the eluting solvent.

(iii) 2,6-Dimethyl-3,4-dinitrophenol (43), m.p. 131.5-132.5° (dec.). (Found: C, 45.0; H, 3.7; N, 13.1. $C_8H_8N_2O_5$ requires C, 45.3; H, 3.8; N, 13.2%). ν_{max} (Nujol)

3500, OH; 1540, 1535, 1320 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.23, s, Me; 2.42, s, Me; 8.05, s, H5. ^{13}C n.m.r. (CD_3COCD_3) δ 11.5, 16.6, methyls; 119.4, C2; 126.6, C5; 127.8, C6; 160.6, C1; Signals for C3 and C4 were not observed.

(iv) *r*-2,*t*-6-Dihydroxy-2,6-dimethyl-4,*t*-5-dinitrocyclohex-3-enone (44), m.p. 153-155° (dec.). (Found C, 38.9, H, 4.1; N, 11.2. $C_8H_{10}N_2O_7$ requires C, 39.0; H, 4.1; N, 11.4%). ν_{max} (Nujol) 3450, OH; 1745, 1733, C=O; 1590, 1575, 1360, 1330 cm^{-1}, NO_2. ^1H n.m.r. (CD_3COCD_3) 1.67, s, Me; 1.75, s, Me; 6.26, d, $J_{5,3}$ 1.5 Hz; 7.78, d, $J_{3,5}$ 1.5 Hz, H3. Structure determined by X-ray crystal structure analysis (see Appendix II).

Nitration of 2,6-Dimethyl-4-nitrophenol (40a) with Fuming Nitric Acid in Acetic Acid

To a stirred suspension of the phenol (40a)(1g) in acetic acid (3ml) at 5° was added dropwise fuming nitric acid (d 1.5; 2ml) over 20 minutes. The nitric acid and acetic acid were then removed under reduced pressure to give a yellow solid residue (*c*.1.6g). This material was shown (^1H n.m.r.) to be a mixture containing the compounds (41) (32%), (42)(26%), (43)(19%) and (44)(16%).

Attempted Preparation of 4,4-Dinitro-2,6-dimethylcyclohexa-2,5-dienone

To a stirred solution of 2,6-dimethyl-4-nitrophenol (40a) (0.5g) in acetic acid (30ml) at 5° was added dropwise 1.1ml of a nitrating mixture (fuming nitric acid (d 1.5; 1ml) and

acetic acid (9 ml)). The resulting mixture was stirred for 10 minutes at 20°, poured into excess water and the precipitate isolated by filtration. The pale yellow solid (230mg) isolated was unreacted starting material, 2,6-dimethyl-4-nitrophenol (40a).

4-Bromo-2,6-dimethylphenol (40c)[83]

Bromine (13.3g) was added slowly to a stirred solution of 2,6-dimethylphenol and acetic acid (80ml), kept at room temperature in a darkened flask. After stirring for 1h., the reaction mixture was poured into water and the precipitate filtered, washed with water and air dried. Recrystallization of this solid from petroleum ether yielded 4-bromo-2,6-dimethylphenol (40c)(94%), m.p. 79-80° [lit.[83] 80-81°]. ν_{max} (Nujol) 3400, OH; 1610 cm^{-1}, C=C. ^1H n.m.r. ($CDCl_3$) δ 2.12, 6H, methyls; 7.10, 2H, H3/H5.

Nitration of 4-Bromo-2,6-dimethylphenol (40c) with Fuming Nitric Acid in Acetic Acid

(a) Addition of phenol (40c) to the mixed acids - The phenol (40c)(1g) was added over 30 minutes to a stirred, cooled (0°) solution of fuming nitric acid (d 1.5; 2.5ml) in acetic acid (3ml). The resulting solution was stirred at 20° for 10 minutes, and the nitric acid and acetic acid then removed under reduced pressure to give as a residue a yellow solid (*c*.1.6g).

Fractional crystallization from dichloromethane/pentane mixtures and separation by h.p.l.c. using a preparative Merck Lobar cyanopropyl column, with hexane/propan-2-ol (4:1) as the eluting solvent, gave the following compounds. The yields are determined by various methods (indicated below).

c-6-Hydroxy-2,6-dimethyl-*r*-2,4,*c*-5-trinitrocyclohex-3-enone (41) (2%; yield isolated), identical with authentic material.

t-6-Hydroxy-2,6-dimethyl-*r*-2,4,*t*-5-trinitrocyclohex-3-enone (42) (2%; yield isolated), identical with authentic material.

4-Bromo-2,6-dimethyl-2,5,6-trinitrocyclohex-3-enone (55) (obtained only in impure state; yield estimated *c*.24% on the basis of ^{1}H n.m.r. spectrum of original mixture). ν_{max} (Nujol) 1760, C=O; 1644, C=C; 1573, 1320 cm^{-1}, NO_2. ^{1}H n.m.r. (CD_3COCD_3) δ 2.18, s, Me; 2.33, s, Me; 6.60, s, H5; 7.25, s, H3. On storage in D_6-acetone this compound decomposed quantitatively to give 2,6-dimethyl-3,4-dinitrophenol (43), identical with authentic material.

4-Bromo-*c*-6-hydroxy-2,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (53) (16% yield; isolated material and estimated by

^{1}H n.m.r. of mixtures with (41), (42) and (54)), m.p. 128-130° (dec.). (Found: 31.0; H, 3.3; Br, 25.5; N, 8.8. $C_8H_9BrN_2O_6$ requires C, 31.0; H, 2.9; Br, 25.8; N, 9.1%). ν_{max} (Nujol) 3500, OH; 1744, C=O; 1577, 1555, 1364, 1318 cm^{-1}, NO_2. ^{1}H n.m.r. (CD_3COCD_3) δ 1.73, s, C6-Me; 2.05, s, C2-Me; 5.83, s, H5; 7.08 s, H3.

4-Bromo-*t*-6-hydroxy-2,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (54) (20% yield; isolated material and estimated by ^{1}H n.m.r. spectra of mixtures with (53) and (58)), m.p. 108-109° (dec.). ν_{max} (Nujol) 3520, OH; 1750, C=O; 1650, C=C; 1570, 1350, 1332 cm^{-1}, NO_2. ^{1}H n.m.r. (CD_3COCD_3) δ 1.63, s, C6-Me; 2.05, s, C2-Me; 5.87, s, H5; 7.23, s, H3. Structure determined by X-ray crystal structure analysis (see Appendix II).

2,6-Dimethyl-3,4-dinitrophenol (43), identical with authentic material. This compound (43) was not present in the crude material from the reaction (^{1}H n.m.r.) and has been shown to be formed in the isolation procedure from compound (55).

4-Bromo-2,6-dimethyl-3-nitrophenol (58) (8% yield; estimated from ^{1}H n.m.r. spectrum of crude material from the reaction), m.p. 90-91°. (Found: $M^{+\cdot}$ 244.9683. $C_8H_8Br^{79}NO_3$ requires $M^{+\cdot}$ 244.9688; insufficient for elemental analysis). ν_{max} (Nujol) 3560, OH; 1530, 1350 cm^{-1}, NO_2. ^{1}H n.m.r. (CD_3COCD_3) δ 2.18, s, Me; 2.30, s, Me; 7.38, s, H5.

2,6-Dimethyl-1,4-benzoquinone (59) (12% yield; estimated from ^{1}H n.m.r. spectrum of crude material from the reaction), m.p. 71-71.5° (sub.) [lit.[84] 72-73° (sub.)]. ν_{max} (Nujol) 1660, 1653, C=O; 1618 cm^{-1}, C=C. ^{1}H n.m.r. ($CDCl_3$) δ 2.07, d, $J_{Me,H}$ 1.5 Hz, methyls; 6.57, q, $J_{H,Me}$ 1.5 Hz, H.

(b) Addition of fuming nitric acid to a solution of the phenol (40c) in acetic acid - To a stirred solution of the bromophenol (40c)(1g) in acetic acid (3ml) at 0-5° was added dropwise fuming nitric acid (d 1.5; 2ml) over 30 minutes. The nitric acid and acetic acid were removed under reduced pressure to give a yellow solid residue (*c.*1.4g). The ^{1}H n.m.r. spectrum of this mixture was similar to that from the nitration of 2,6-dimethyl-4-nitrophenol (40a) with fuming nitric acid in acetic acid, above; from the ^{1}H n.m.r. spectra it was estimated that of the products present *c.*90% were nitro-debrominated compounds. Preliminary crystallizations confirmed this.

Reaction of 4-Bromo-2,6-dimethylphenol (40c) with Nitrogen Dioxide in Benzene Solution

A solution of the bromo phenol (40c)(1g) in benzene (10ml), at 8°, was deoxygenated by a stream of pure nitrogen. Nitrogen dioxide was bubbled through the stirred solution for 30s, and the solution stirred under an atmosphere of nitrogen dioxide for 2h. The excess nitrogen dioxide was removed in a stream of nitrogen and the solvent removed under reduced pressure to give a yellow solid residue (*c.* 1.26g). This mixture was shown to consist mainly (*c.* 80%) of nitro-debrominated products, identical with those derived from the reaction of 2,6-dimethyl-4-nitrophenol (40a) with nitrogen dioxide, above.

5.3 Experimental Relating to Chapter 3

Reaction of 2,3,4,6-Tetramethylphenol (71) with Nitrogen Dioxide in Benzene

A solution of the tetramethylphenol (71)(500 mg) in benzene (5 ml) was deoxygenated with a stream of pure nitrogen and cooled to 8°C. Nitrogen dioxide was bubbled through the stirred suspension for 30s, and the mixture then stirred under an atmosphere of nitrogen dioxide for a further 2 h. The excess nitrogen dioxide was removed in a stream of nitrogen, and the solvent removed under reduced pressure. The residue was a pale yellow oil (912 mg) which was shown, by infrared and ^1H n.m.r. spectra, to be essentially a mixture of six components.

The crude product was adsorbed onto a Chromatotron silica gel plate. Elution with ether/petroleum ether mixtures and methanol gave the following compounds (yields isolated are recorded) in elution order:

4-Hydroxy-2,4,5,6-tetramethyl-5,6-dinitrocyclohex-2-enone (72)(24%) [eluted by ether/petroleum ether (1:20)], an unstable oil, which decomposed at 20° to give 4-hydroxy-2,3,4,6-tetramethylcyclohexa-2,5-dienone (73), ν_{max} (liquid film) 3500, OH; 1683, 1655, 1648, 1636, conjugated ketone; 1560, 1552 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.85, s, 3H, Me; 1.95, bs, 9H, methyls; 6.62, q, $J_{3,Me}$1.5 Hz, H3. λ_{max} ($CHCl_3$) 242.5 nm (ε 9600). Decomposition of the hydroxy dinitroketone (72) gave the 4-hydroxy-2,3,4,6-tetramethylcyclohexa-2,5-dienone (73), m.p. 88-89°. (Found: C, 72.2; H, 8.5. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%). ν_{max} (Nujol) 3440, OH; 1673, 1628 cm^{-1}, cross-conjugated dienone. ^1H n.m.r. ($CDCl_3$) δ 1.40, s, C4-Me; 1.85, 1.87, each s, C2-, C3-Me; 2.03, d, $J_{Me,5}$ 1.6 Hz, C6-Me;

6.65, q, $J_{5,Me}$ 1.6 Hz, H5. $\lambda_{max}(CHCl_3)$ 245, 279 (ε 13000, 2800).

2,4,5,6-Tetramethyl-*r*-2,*t*-5,*c*-6-trinitrocyclohex-3-enone (74)(11%) [eluted by ether/petroleum ether (1:4)], m.p. 104-105° (dec.). ν_{max} (Nujol) 1758, α,α'-dinitro ketone; 1698, C=C; 1565, 1556 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.83, s, Me; 1.92, s, Me; 2.00, s, Me; 2.02, d, $J_{Me,3}$ 1 Hz, C4-Me; 6.47, q, $J_{3,Me}$ 1 Hz, H3. The structure of trinitro ketone (74) was determined by X-ray crystal structure analysis (see Appendix II).

2,4,5,6-Tetramethyl-*r*-2,*c*-5,*t*-6-trinitrocyclohex-3-enone (75)(10%) [eluted by ether/petroleum ether (3:7)], m.p. 84-85° (dec.). (Found: C,42.2; H, 4.5; N, 14.6. $C_{10}H_{13}N_3O_7$ requires C, 41.8; H, 4.6; N, 14.6%). ν_{max} (Nujol) 1750, α,α'-dinitro ketone; 1570, 1550 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$)δ 1.93, s, Me; 1.97, s, Me; 2.07, 2.08, s and d, 6H, methyls; 6.30, q, $J_{3,Me}$ 1 Hz, H3.

2,4,5,6-Tetramethyl-*r*-4,*t*-5,*t*-6-trinitrocyclohex-2-enone (82)(5%) [eluted by ether/petroleum ether (1:1)], m.p. 108-110° (dec.). ν_{max} (Nujol) 1715, α'-nitro conjugated ketone; 1560 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$)δ 1.78, s, Me; 1.91, s, Me; 1.92, s, Me; 2.13, d, $J_{Me,3}$ 1.6 Hz, C2-Me; 6.40, q, $J_{3,Me}$ 1.6 Hz, H3. λ_{max} ($CHCl_3$) 242.5 nm (ε 5100). The structure of trinitro ketone (82) was determined by X-ray crystal structure analysis (see Appendix II).

2,4,5,6-Tetramethyl-*r*-2,*t*-5,*t*-6-trinitrocyclohex-3-enone (76)(12%) [eluted by ether], m.p. 121-121.5° (dec.). (Found: C, 42.0; H, 4.7; N, 14.4. $C_{10}H_{13}N_3O_7$ requires C, 41.8; H, 4.6; N, 14.6%). ν_{max} (Nujol) 1760, α,α'-dinitro ketone; 1576, 1572, 1560 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$)δ 1.87

s, Me; 1.90, s, Me; 2.02, d, $J_{Me,3}$ 1.7 Hz, C4-Me; 2.07, s, Me; 6.33, q, $J_{3,Me}$ 1.7 Hz, H3.

2,4,5,6-Tetramethyl-*r*-2,*c*-5,*c*-6-trinitrocyclohex-3-enone (77)(13%) [eluted by methanol/ether (1:9)], m.p. 133-133.5° (dec.). (Found: C, 41.9; H, 4.8; N, 14.6. $C_{10}H_{13}N_3O_7$ requires C, 41.8; H, 4.6; N, 14.6%). ν_{max} (Nujol) 1762, α,α'-dinitro ketone; 1578, 1573, 1554 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.85, s, Me; 1.95, s, Me; 2.02, s, Me; 2.05, d, $J_{Me,3}$ 1.5 Hz, C4-Me; 6.27, q, $J_{3,Me}$ 1.5 Hz, H3.

Nitration of 1,2,3,5-Tetramethylbenzene (66a)

Fuming nitric acid (d 1.5; 16.8 ml) was added dropwise to a stirred solution of 1,2,3,5-tetramethylbenzene (66a) (20 g) in dichloromethane (45 ml) at -5-0°C over 30 minutes. After stirring for 1h at room temperature the mixture was poured into an excess of iced water. The organic layer was washed several times with water and dilute aqueous sodium bicarbonate solution before drying over anhydrous sodium sulphate. The solvent was removed under reduced pressure leaving a yellow/brown oil (*c.* 27 g) which was shown, by ^1H n.m.r., to be a complex mixture. Part of this mixture (16 g) was separated by column chromatography using silica gel followed by further separation on a Harrison 7924 Chromatotron.

The following compounds, listed with their isolated yields were eluted from the chromatotron in the order given.

1,2,3,5-Tetramethylbenzene (66a)(3%), identical with authentic material.

2,3,4,6-Tetramethyl-1-nitrobenzene (85)(25%), m.p. 138-139° [lit.[85] 139°]. (Found: C, 67.2; H, 7.4; N, 7.6. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%). ν_{max} (Nujol) 1530, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.18, 9H, methyls; 2.28, 3H, Me; 6.93, s, H5.

3,4,5-Trimethylphenylnitromethane (86)(4%), m.p. 64-65° [lit.[86] 63-65°]. (Found: C,66.8; H, 7.4; N, 7.7. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%). ν_{max} (Nujol) 1560, 1360 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.18, Me; 2.28, 6H, methyls; 5.32, $C\underline{H}_2NO_2$; 7.08, 2H, aromatic protons. ^{13}C n.m.r. ($CDCl_3$) δ 15.4, C4-methyl; 20.5, C3/C5-methyls; 80.0, $\underline{C}$-NO_2; 126.6, C3/C5; 129.0, C2/C6; 137.3, C4.

3,4,5-Trimethylbenzaldehyde (87)(19%), m.p. 60.5-61° [lit.[86] 62.0-62.3°]. (Found: C, 81.2; H, 8.3, $C_{10}H_{12}O$ requires C, 81.0; H, 8.2%). ν_{max} (Nujol) 1705 cm^{-1}, C=O. ^1H n.m.r. ($CDCl_3$) δ 2.23, Me; 2.35, 6H, methyls; 7.52, 2 H, aromatic protons; 9.92, $C\underline{H}O$. ^{13}C n.m.r. ($CDCl_3$) δ 16.0, C4-methyl; 20.4, C3/C5-methyls; 128.8, C2/C6; 133.9, C1; 137.3, C3/C5; 142.9, C4; 192.3, $H\underline{C}$=O.

3,4,5-Trimethylbenzoic acid (88)(1%), m.p. 214-215° [lit.[87] 215-216°]. (Found: C, 72.9; H, 7.5. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.4%). ν_{max} (Nujol) 3250-2400, $-CO_2H$; 1675 cm^{-1}, C=O. ^1H n.m.r. ($CDCl_3$) δ 2.25, Me; 2.35, 6H, methyls; 7.78, 2H, aromatic protons.

2,3,5-Trimethylbenzoic acid (89)(0.3%), m.p. 133-135° [lit.[88] 127°]. ν_{max} (Nujol) 3250-2400, $-CO_2H$; 1692 cm^{-1}, C=O. ^1H n.m.r. ($CDCl_3$) δ 2.28, 6H, methyls; 2.58, Me; 7.05, H4; 7.85, H6.

2,4,6,6-Tetramethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (92) (1.3%), m.p. 72-73° (dec.). ν_{max} (Nujol) 1738, α-nitro

ketone; 1568, 1550, 1362, 1332 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.27, Me; 1.33, Me; 1.95, Me; 2.07, d, $J_{Me,3}$ 1.8 Hz, C4-Me; 4.95, s, H5; 6.25, q, $J_{3,Me}$ 1.8 Hz, H3. The structure of the dinitroketone (92) was determined by X-ray crystal structure analysis (see Appendix II).

2,4,6,6-Tetramethyl-*r*-4,*t*-5-dinitrocyclohex-2-enone (93) (0.1%), m.p. 80-82° (dec.). ν_{max} (Nujol) 1700, 1658, conjugated ketone; 1577, 1558, 1350, 1328 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ1.12, Me; 1.25, Me; 1.78, Me; 2.03, d, $J_{Me,H3}$ 2.0 Hz, C2-Me; 5.78, d, $J_{5,3}$ 2 Hz, H5; 6.53, dq, $J_{3,Me} = J_{3,5} =$ 2 Hz, H3. The structure of dinitroketone (93) was determined by X-ray crystal structure analysis (see Appendix II).

4-Hydroxy-2,3,4,6-tetramethylcyclohexa-2,5-dienone (73) (0.3%), identical with authentic material, above.

2,4,5,6-Tetramethyl-*r*-2,*t*-5,*c*-6-trinitrocyclohex-3-enone (74)(0.6%), identical with authentic sample, above.

2,4,5,6-Tetramethyl-*r*-2,*c*-5,*t*-6-trinitrocyclohex-3-enone (75)(0.4%), identical with authentic sample, above.

c-6-Hydroxy-2,4,5,6-tetramethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (96) (0.05%), m.p. 80-81°. ν_{max} (Nujol) 3500, OH; 1740, α-nitro ketone; 1560, 1360 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) 1.40, Me; 1.83, Me; 1.95, Me; 1.98, d, $J_{Me,3}$ 1.6 Hz, C4-Me; 5.27, q, $J_{3,Me}$ 1.6 Hz, H3. The structure of hydroxy-dinitroketone (96) was determined by X-ray crystal structure analysis (see Appendix II).

4-Hydroxy-2,3,4,6-tetramethyl-5-nitrocyclohexa-2,5-dienone (95)(0.3%), m.p. 141-143°. (Found: C, 57.1; H, 6.3; N, 6.6. $C_{10}H_{13}NO_4$ requires C,56.9; H, 6.2; N, 6.6%). ν_{max} (Nujol) 3470, OH; 1680, 1632, cross-conjugated dienone; 1556 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ1.50, Me; 1.88, Me; 2.12

6H, methyls. λ_{max} ($CHCl_3$) 244, 281 nm (ε 9500, 3200).

1,2,3,5,6,7-Hexamethyl-9,10-anthraquinone (90)(0.2%), m.p. 243-244° (sub.). (Found: $M^{+}\cdot$, 292.143. Calc. for $C_{20}H_{20}O_2$ $M^{+}\cdot$, 292.146. 277, $M^{+}-CH_3$; 262, $277-CH_3$; insufficient for elemental analysis). ν_{max} (Nujol) 1665, 1655 cm^{-1}, quinone. ^1H n.m.r. ($CDCl_3$) δ 2.30, 6H, methyls; 2.42, 6H, methyls; 2.72, 6H, methyls; 7.90, 2H, H4, H8. λ_{max} ($CHCl_3$) 273, 289, 350 nm (ε 30600, 10500, 3800).

r-2-Hydroxy-2,4,6,6-tetramethyl-*t*-5-nitrocyclohex-3-enone (94)(0.3%), m.p. 131-132°. ν_{max} (Nujol) 3480, OH; 1712, α-hydroxy ketone; 1685, C=C; 1568 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.22, Me; 1.35, Me; 1.55, Me; 1.97, d, $J_{Me,3}$ 1.8 Hz, C4-Me; 4.87, s, H5; 5.98, q, $J_{3,Me}$ 1.8 Hz, H3. The structure of hydroxy nitro ketone (94) was determined by X-ray crystal structure analysis (see Appendix II).

2,4,5,6-Tetramethyl-*r*-2,*t*-5,*t*-6-trinitrocyclohex-3-enone (76)(1%), identical with an authentic sample, above.

2,4,6,6-Tetramethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (91)(1%), m.p. 134-135° [lit.[74,75] 137-138°] ν_{max} (Nujol) 1737, α-nitro ketone; 1572, 1555 cm^{-1}, NO_2. [lit.[74,75] ν_{max} (Nujol) 1738, C=O; 1573, 1555 cm^{-1}, NO_2]. ^1H n.m.r. ($CDCl_3$) δ 1.28, Me; 1.32, Me; 1.90, Me; 2.10, d, $J_{Me,3}$ 1 Hz, C4-Me; 4.95, s, H5; 6.10, q, $J_{3,Me}$ 1 Hz, H_3. [lit.[74,75] ^1H n.m.r. ($CDCl_3$) δ 1.28, 1.31, 1.89, 2.10, d, methyls; 4.95, s, H5; 6.08, q, H3].

Attempted Preparation of 4-Nitro-2,3,4,6-tetramethylcyclohexa-2,5-dienone

To a stirred solution of 2,3,4,6-tetramethylphenol (71) (1g) in glacial acetic acid (3 ml) at 10°C was added dropwise

2.8 ml of a nitrating mixture [fuming nitric acid (1 ml), acetic acid (9 ml)]. Upon completion of the nitric acid addition the resulting mixture was poured into iced water (50 ml). The aqueous solution was extracted with ether which was washed free of acid, dried over magnesium sulphate and the solvent removed under reduced pressure. The product was a yellow oil which was shown by infrared and ^{1}H n.m.r. spectra to be a complex mixture containing little if any nitro dienone. Preliminary separation techniques confirmed this observation.

5.4 Experimental Relating to Chapter 4

Nitration of 1,2,3-Trimethylbenzene[77]

To a stirred mixture of fuming nitric acid (d 1.5; 10g) and concentrated sulphuric acid (d 1.84; 15g) kept below 10°C, was added dropwise 1,2,3-trimethylbenzene (5g). The reaction mixture was stirred for 2h at less than 10° before being poured into excess ice. The precipitate (10g), which formed, was filtered, washed with water and air dried. Separation by column chromatography using silica gel and mixtures of ether/petroleum ether as the eluting solvents gave the following compounds, given with their isolated yields.

1,2,3-Trimethyl-4,6-dinitrobenzene (103)(61%) [eluted by ether/petroleum ether (1:99)], m.p. 115-112.5° [lit.[89] 112-113°]. ν_{max} (Nujol) 1598, aromatic; 1530, 1330 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.42, 3H, Me; 2.50, 6H, methyls; 8.07, H5. ^{13}C n.m.r. (CD_3COCD_3) δ 16.3 C1/C3-methyls; 16.9, C2-Me; 117.4, C5; 135.3, C1/C3; 142.7, C2; 149.5, C4/C6.

1,2,3-Trimethyl-4,5-dinitrobenzene (107)(14%) [eluted by ether/petroleum ether (1:49)], m.p. 151-152° [lit.[89] 153°]. ν_{max} (Nujol) 1550, 1530, 1325 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.27, 2.35, 2.43, each 3H, methyls; 7.85, H6. ^{13}C n.m.r. (CD_3COCD_3) δ 15.1, 17.0, 20.8, methyls; 117.0, C6; 124.7, C3; 131.2, C5; 136.1, C1; 141.4, C4; 146.7, C2.

1,2,3-Trimethyl-4,5,6-trinitrobenzene (106)(18%) [eluted by ether/petroleum ether (1:1)], m.p. 206-207°. (Found: C, 42.3; H, 3.5; N, 16.3. $C_9H_9N_3O_6$ requires C, 42.4; H, 3.6; N, 16.5%). ν_{max} (Nujol) 1550, 1352, 1338 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.37, 6H, methyls; 2.43, 3H, Me. ^{13} C n.m.r.

(CD_3COCD_3) δ 16.0, Cl/C3-methyls; 17.9, Me; 134.5, Cl/C3; 143.0, C4/C6; 148.9, C2. A signal was not obtained for C5.

Nitration of 1,2,3-Trimethyl Dinitro Benzenes (103) and (107)

General Procedure - To a stirred mixture of fuming nitric acid (d 1.5, 0.7 ml) and concentrated sulphuric acid (d 1.85; 0.8 ml), kept below 10°, add the 1,2,3-trimethyldinitrobenzene (1g). Keep the reaction below 10° for 2h, then pour into ice. Collect the solid by filtration, then wash with water until free of acid and leave to air dry.

1,2,3-Trimethyl-4,6-dinitrobenzene (103)

Treatment of the trimethyldinitrobenzene (103), as above, gave a white solid (950 mg) which was shown to be only unreacted 1,2,3-trimethyl-4,6-dinitrobenzene (103).

1,2,3-Trimethyl-4,5-dinitrobenzene (107)

Treatment of the trimethyldinitrobenzene (107), as above, gave a white solid (930 mg) which was shown by ^1H n.m.r. to be a mixture (1:1) of 1,2,3-trimethyl-4,5-dinitrobenzene (107) and 1,2,3-trimethyl-4,5,6-trinitrobenzene (106).

Nitration of 1,2,3-Trimethyl-4,6-dinitrobenzene (103) with Fuming Nitric Acid

1,2,3-Trimethyl-4,6-dinitrobenzene (103)(2g) was added slowly to cold (0°), stirred fuming nitric acid (d 1.5; 16 ml). The reaction mixture was stoppered and left at room temperature for 126 days. The acid was removed by distillation under reduced pressure giving a pale yellow solid (2.45g).

Methylene chloride was added to 1 g of the product mixture

and removed after five minutes leaving a white solid (340 mg). Recrystallization of this material from ether/pentane yielded firstly oxalic acid dihydrate, (160 mg), m.p. 99-100° [lit.[58] 101.5° (hyd)]. ν_{max} (Nujol) 3400, OH(br); 1690 cm^{-1}, C=O (br). The remaining material (160 mg) was dimethylpropanedioic acid (108), m.p. 202-202.5° [lit.[90] 192°]. ν_{max} (Nujol) 2200-3600, CO_2H; 1690-1710 cm^{-1}, C=O. ^1H n.m.r. (DMSO) δ 1.30 [lit.[90] (DMSO) δ 1.32]; (CD_3COCD_3) δ 1.43.

Further addition and removal of methylene chloride to the product mixture yielded another 53 mg of dimethylpropanedioic acid (108).

Fractional recrystallization from ether/pentane of the remaining material gave firstly 2,6-dimethyl-3,5-dinitrobenzoic acid (109) (50 mg, 9%), m.p. 190-191°. (Found: C, 44.9; H, 3,3; N, 11.6. $C_9H_8N_2O_6$ requires C, 45.0; H, 3.4; N, 11.7%). ν_{max} (Nujol) 2200-3200, CO_2H; 1718, C=O; 1600, aromatic; 1530, 1335 cm^{-1}, NO_2. ^1H n.m.r. (CD_3COCD_3) δ 2.52, 6H, methyls; 8.50, aromatic proton, H4.

Further recrystallization yielded 4-hydroxy-3,4,5-trimethyl-2,6-dinitrocyclohex-2,5-dienone (110) (42 mg, 8%), m.p. 211-211.5° [lit.[78] 213°]. ν_{max} (Nujol) 3470, OH; 1675, 1650, cross-conjugated dienone; 1552, 1542 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ1.65, 3H, Me; 2.22, 6H, methyls; (CD_3COCD_3) δ 1.72, Me; 2.23, 6H, methyls.

The remaining material was shown to be 1,2,3-trimethyl-4,6-dinitrobenzene (103)(346 mg, 35%), identical with authentic material.

Attempted Nitration of 1,2,3-Trimethyl-4,5,6-trinitrobenzene (106) With Fuming Nitric Acid

1,2,3-Trimethyl-4,5,6-trinitrobenzene (106)(2g) was added slowly to cold (0°), stirred fuming nitric acid (d 1.5; 16 ml). The solution was stored, in a sealed flask, at approx. 20° for 131 days. The acid was removed by distillation under reduced pressure. The product obtained (1.96g) was unreacted starting material, 1,2,3-trimethyl-4,5,6-trinitrobenzene (106) identical with authentic material.

Bromination of 1,2,3-Trimethylbenzene[79]

To a stirred, cooled (0°) solution of 1,2,3-trimethylbenzene (60 ml) in chloroform (100 ml) was added bromine (21 ml), in chloroform (150 ml), over 3h. The solution was stirred at 20° for 24h, and the solvent was then removed by distillation, and the residue dried over magnesium sulphate and fractionated under reduced pressure (15 mm. Hg). The fraction collected at 135° was 1-bromo-2,3,4-trimethylbenzene (66g), b.p. 229° [lit.[79] 229.5]. ^{1}H n.m.r. ($CDCl_3$) δ 2.13, s, 6 H; 2.28, s, 3H; 6.74, d, $J_{H,H}$ 8 Hz, H5; 7.24, d, $J_{H,H}$ 8 Hz, H6.

Nitration of 1-Bromo-2,3,4-trimethylbenzene[79]

To a stirred solution of fuming nitric acid (d 1.5; 30 ml) and concentrated sulphuric acid (d 1.84; 60 ml) at 0° was added dropwise, 1-bromo-2,3,4-trimethylbenzene (20g). After addition was completed the reaction mixture was poured onto ice. The precipitate formed, was separated by filtration and washed with water. The crude material (*c.* 27g) was separated by column chromatography using 5% deactivated alumina and mixtures of ether/petroleum ether as the eluting solvents. Compounds are given with their isolated yields.

Elution with ether/petroleum ether (1:99) gave 1-bromo-2,3,4-trimethyl-5-nitrobenzene (115)(12%), m.p. 83° [lit.[91] 82-83°]. ν_{max} (Nujol) 1535, 1353 cm^{-1}, NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 2.35, 6H, methyls; 2.45, 3H, Me; 7.83, aromatic proton, H6. ^{13}C n.m.r. (CD_3COCD_3) δ 15.8, 17.63, 20.7, methyls; 122.4, C1; 125.2, C6; 130.1, C4; 140.8, C3; 141.6, C2; 150.2, C5.

Further elution with ether/petroleum ether (1:99) gave 1-bromo-2,3,4-trimethyl-6-nitrobenzene (116)(10%), m.p. 120-120.5°. (Found: C, 44.3; H, 4.2; N, 5.7; Br, 33.0. $C_9H_{10}BrNO_2$

requires C, 44.3; H, 4.1; N, 5.7; Br, 32.7%). ν_{max} (Nujol) 1530, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.32, 6H, methyls; 2.48, 3H, Me; 7.35, aromatic proton, H5.

Elution with ether/petroleum ether (1:3) gave the major product, 1-bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105) (75%), m.p. 194-195° [lit.[79,92] 196.5°]. ν_{max} (Nujol) 1545, 1345, 1340 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.30, Me; 2.42, Me; 2.57, Me. ^{13}C n.m.r. ($CDCl_3$) δ 15.9, 18.2, 21.5, methyls; 114.2, C1; 131.0, C4; 143.2, C3; 143.9, C2. Signals were not observed for C5 and C6.

Nitration of Bromopentamethylbenzene[92]

Bromopentamethylbenzene (9.8g) in chloroform (43 ml) was added slowly (2h) to a well stirred mixture of fuming nitric acid (d 1.5; 29 ml) and chloroform (170 ml) at 25-31°. The chloroform layer was separated, washed with sodium carbonate solution (5%) and then washed with water. Removal of the solvent under reduced pressure left a yellow oily solid (9.6g) which yielded as the only product after recrystallization, 1-bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105)(2.6g, 21%).

Attempted Nitration of 1-Bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105)

1-Bromo-2,3,4-trimethyl-5,6-dinitrobenzene (105)(1g) was added slowly to cold (0°), stirred fuming nitric acid (d 1.5; 8 ml). The solution was stored, in a sealed flask, at approximately 20° for 40 days. The reaction mixture was then poured into ice, the precipitate filtered and washed free of acid with water. The solid was unreacted 1-bromo-

2,3,4-trimethyl-5,6-dinitrobenzene (105)(967 mg), identical with authentic material.

Nitration of 1,2,4,5-Tetramethylbenzene[93,94]

A solution of 1,2,4,5-tetramethylbenzene (13.4g) in chloroform (150 ml) was added to concentrated sulphuric acid (75 ml). The stirred mixture was cooled, then slowly nitrated with fuming nitric acid (d 1.5; 6g), the temperature being kept below 50°. The acid layer was removed and the chloroform layer washed with sodium carbonate solution and water, then dried over magnesium sulphate. The chloroform was removed under reduced pressure and the 1,2,4,5-tetramethyl-3,6-dinitrobenzene (117)(13.7g; 60%) obtained as white crystals on crystallization from methanol, m.p. 208-208.5° [lit.[93] 207.5°]. ν_{max} (Nujol) 1530, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.32, methyls. ^{13}C n.m.r. ($CDCl_3$) δ 14.54, methyls; 126.99, C-Me; 153.08, C-NO_2.

Nitration of 1,2,4,5-Tetramethyl-3,6-dinitrobenzene (117)

1,2,4,5-Tetramethyl-3,6-dinitrobenzene (117)(1g) was added to cold (0°), stirred fuming nitric acid (d 1.5, 8 ml). The reaction mixture was stoppered and left at room temperature for 156 days. The white crystalline solid (560 mg) which formed was isolated by filtration. Recrystallization of this material from methylene chloride/pentane revealed that it consisted mostly of 2,4,5-trimethyl-3,6-dinitrobenzoic acid (118), m.p. 207-208°. (Found: C, 47.6; H, 4.3; N, 11.1. $C_{10}H_{10}N_2O_6$ requires C, 47.3; H, 4.0; N, 11.0%). ν_{max} (Nujol) 2200-3300, CO_2H; 1700, C=O; 1535, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 2.28, 3H, Me; 2.36, 6H, methyls. ^{13}C n.m.r. (CD_3COCD_3) δ 14.91, 15.14, 15.26, methyls; 127.39, C1; 130.60, C5; 133.27, C2; 151.11, C4; 154.29, C3; 165.09, C6.

The remainder of this material was unreacted 1,2,4,5-tetramethyl-3,6-dinitrobenzene (117), identical with authentic material above. The proportion of 1,2,4,5-tetramethyl-3,6-dinitrobenzene (117) to the 2,4,5-trimethyl-3,6-dinitrobenzoic acid (118) from ^{1}H n.m.r. spectroscopy, was (1:7).

The nitric acid was removed from the remaining material, under reduced pressure, to give a solid residue (420 mg). Fractional crystallization of this material, from dichloromethane, gave dimethylpropanedioic acid (108) (60 mg), identical with authentic material, above, and (E)-2,4,4-trimethyl-3-nitropent-2-ene-1,5-dioic acid (119) (162 mg), m.p. 131-133°. (Found: C, 44.3; H, 5.2; N, 6.3. $C_8H_{11}NO_6$ requires C, 44.2; H, 5.1; N, 6.5%). ν_{max} (Nujol) 3700-2200, CO_2H; 1720, C=O; 1710, C=O; 1650, C=C; 1543, 1525, 1360 cm^{-1}, NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.57, s, 6H, C4-Me's; 1.95, s, 3H, C2-Me. ^{13}C n.m.r. (CD_3COCD_3) δ 16.7, 2-$\underline{C}H_3$; 25.7, 4,4-$\underline{\underline{C}}H_3$; 46.1, C4; 124.9, C2; 174.2, 176.9, $\underline{\underline{C}}O_2H$. λ_{max} ($CHCl_3$) 242 nm (ε 2000).

The residues from the above fractional crystallizations were combined and the components of the mixture (183 mg) were separated on a Chromatotron silica gel plate to give in order of elution:

1,2,4,5-tetramethyl-3,6-dinitrobenzene (117)(23 mg),

2,4,5-trimethyl-3,6-dinitrobenzoic acid (118)(14 mg)

(E)-2,4,4-trimethyl-3-nitropent-2-ene-1,5-dioic acid (119)(125 mg).

All samples were identical with authentic material. The overall yields of products were 2,4,5-trimethyl-3,6-dinitrobenzoic acid (118)(49%), (E)-2,4,4-trimethyl-3-

nitropent-2-ene-1,5-dioic acid (119)(33%) and dimethyl-propanedioic acid (108)(11%).

APPENDIX I

NITRATION OF 2,4-DIMETHYL-6-NITROPHENOL

Introduction

The nitration of 4-cyclopropyl-2-methyl-6-nitrophenol (122) with nitric acid in acetic acid has been reported[95] to yield only the hydroxy trinitrocyclohex-2-enone (123) (41%), the structure of which was determined by X-ray crystal structure analysis. The proposed mechanism, outlined in Scheme 30, involves initial formation of the 4-nitro dienone (124). The formation of the cyclohex-2-enone (123) was envisaged as occurring by addition of the elements of nitric acid to this 4-nitro dienone (124). In view of the examples discussed previously in Chapter 2, this mechanism seems improbable as a description of the reaction pathway followed in this nitration.

A more probable reaction pathway, given in Scheme 31, involves initial formation of the 6-nitro dienone (125). Rearrangement of this 6-nitro dienone (125), *via* the 6-nitrito dienone, would then give the 6-hydroxy dienone (126). As shown in Scheme 31, 6-hydroxy dienone (126) exists in a conformation determined by intramolecular carbonyl-hydroxyl hydrogen bonding. In this conformation one face of the diene system is shielded by the C6-methyl group. Consequently $^{\bullet}NO_2$ attack at C5 of the diene system occurs on the less hindered face of the molecule *cis-* to the C6-hydroxyl group. This relative *cis-* stereochemistry of the C5-nitro group and C6-hydroxyl group is observed both in compound (123) and in all reported cyclohexenones thought to arise *via* nitrogen dioxide

addition to a 6-hydroxy dienone (refer Chapter 2). Subsequent addition of $^{\cdot}NO_2$ to the delocalised radical intermediate (127) would then give the isolated compound (123).

In view of the reservations expressed above an examination of the nitration of the analogous 2,4-dimethyl-6-nitrophenol (128) was undertaken. Further, 2,4-dimethyl-6-nitrophenol (128) differs from 2,6-dimethyl-4-nitrophenol (40a) (discussed in Chapter 2) only in the relative positions of the C4- and C6-methyl and nitro groups. It was therefore of interest to investigate the effect of this transposition of functionality.

Nitration of 2,4-Dimethyl-6-nitrophenol (128) in Fuming Nitric Acid

A solution of the phenol (128) in cold (0^{o}) dichloromethane, was nitrated with fuming nitric acid. Removal of the solvent and nitric acid, under reduced pressure, gave a yellow oily solid which was shown (^{1}H n.m.r.) to be essentially a mixture of five compounds (129)(11%), (130)(36%), (131)(13%), (132)(11%) and (133)(19%). After storage of this mixture in deuterio-acetonitrile at 30^{o} for 24h it was shown (^{1}H n.m.r.) to consist of (129)(15%), (130)(37%), (131)(31%) and (132)(16%). These results indicate that compound (133) was decomposing to give, most probably, compounds (131) and (132).

Attempts at isolating all compounds by fractional crystallization and chromatographic techniques were not successful because of the instability of the compounds present. Structural assignments are, therefore, made largely on the basis of spectroscopic data and a consideration of likely reaction pathways.

The 1,4-benzoquinone derivatives, (129) and (130), were

isolated by a combination of fractional crystallization and chromatography on a Chromatotron silica gel plate. Both (129) and (130) are known compounds[96] and their structural assignments are supported by their spectroscopic data.

The two C4-epimeric cyclohex-2-enones (131) and (132) were assigned structures on the basis of their spectroscopic data and from a consideration of their likely mode of formation, see below. Both compounds, (131) and (132), are assigned the relative *cis*-C5-nitro/C6-hydroxy stereochemistry which is a feature of all cyclohexenones arising from nitrogen dioxide addition to a 6-hydroxy cyclohexa-2,4-dienone. This assignment is consistent with the isolation of only two cyclohex-2-enones. Compound (131) was tentatively assigned the *cis*-4-nitro/5-nitro stereochemistry on the basis of its H3 chemical shift (δ 8.03) which is virtually identical to the H3 resonance for the 4-cyclopropyl hydroxy trinitrocyclohex-2-enone (122) (δ 8.01). The infrared spectrum of compound (131) indicates a hydroxyl function (ν_{max} 3550 cm^{-1}) and a conjugated carbonyl function bearing an α-nitro group (ν_{max} 1737 cm^{-1}). The ^1H n.m.r. spectrum indicates the presence of two methyl groups, a vinylic proton (see above) and a $C\underline{H}NO_2$ function. The methyl resonances are reasonable for a methyl group geminal to a hydroxy group (δ 1.67) and for a methyl group geminal to a nitro group (δ2.18). The olefinic proton H3, coupled to H5 ($J_{H3,H5}$ 1.8 Hz), has a chemical shift (δ 8.03) consistent with having a nitro group on the double bond at C2.

Compound (132), was obtained only as a mixture with compounds (130) and (131)(1:1:2). Its structure, C4-epimeric to that of compound (131), was assigned on the basis of its ^1H n.m.r. spectrum and by analogy to compound (131). The

^{1}H n.m.r. resonances for compound (132) are similar to those of compound (131) indicating the presence of the same broad structural features *i.e.* a methyl geminal to a hydroxy group (δ 1.42), a methyl group geminal to a nitro group (δ 1.98), H5 geminal to a nitro group (δ 5.92) and coupled to H3 ($J_{H5,H3}$ = 2.0 Hz), a proton vicinal to the C2-nitro group (δ 7.70). The minor differences in the spectroscopic data for compounds (131) and (132) are consistent with their assignment as C4-epimers.

The cyclohex-3-enone (133), obtained by fractional crystallization (*c.* 80% pure), was assigned its structure on the basis of its spectroscopic data and on consideration of its likely mode of formation. The infrared spectrum indicates the presence of a hydroxyl function (ν_{max} 3500 cm^{-1}) and the carbonyl stretching frequency of 1760 cm^{-1} is consistent only with the α,α-dinitro non-conjugated ketone structure proposed. The ^{1}H n.m.r. spectrum for compound (133) indicates the presence of two methyl groups, one geminal to a hydroxy group (δ 1.52), and one vinylic and coupled to the olefinic proton H3 (δ 2.20, $J_{Me,H3}$ = 1.8 Hz). The chemical shift (δ 5.58) for H5 is consistent with its location geminal to a nitro group. On storage in deuterioacetonitrile, the hydroxy trinitro ketone (133) was shown to decompose quantitatively to give a mixture (*c.* 2:1) of compounds (131) and (132). The implications of this conversion are included in a discussion of the reaction mechanism, below.

Nitration of 2,4-Dimethyl-6-nitrophenol (128) in Nitrogen Dioxide

Reaction of the phenol (128) with nitrogen dioxide was

carried out in benzene solution. The crude residue obtained, after removal of the solvents was shown (^{1}H n.m.r.) to be a mixture of (129)(12%), (130)(4%), (131)(24%), (132)(12%) and (133)(40%).

Reaction Pathways in the Nitration of 2,4-Dimethyl-6-nitrophenol (128)

The reactions of the 6-nitro phenol (128) with fuming nitric acid or nitrogen dioxide are envisaged as occurring by the reaction pathways summarised in Scheme 32. The initially formed 6-nitro dienone (134) is seen as rearranging *via* the corresponding 6-nitrito dienone, to give the 6-hydroxy dienone (135). Attack by $^{\cdot}NO_2$ at C5 of the hydroxy dienone (135) would give the delocalised radical intermediate (136) with the *cis*-5-nitro/6-hydroxy stereochemistry. This radical intermediate (136) can then undergo further addition of $^{\cdot}NO_2$ either at C4 to give both possible C4-epimeric cyclohex-2-enones (131) and (132), or at C2 to give the 2,2,5-trinitrocyclohex-3-enone (133). The ratio of addition at C2 to that at C4 is approximately (1:1) for reaction of the nitro phenol (128) with nitrogen dioxide.

The rearrangement of the trinitrocyclohex-3-enone (133) in deuterioacetonitrile to give the C4-epimeric trinitrocyclohex-2-enones (131) and (132) is envisaged as occurring by a radical dissociation - recombination process (Scheme 33). Dissociation of (133) to give the radical intermediate (136) and nitrogen dioxide is followed by recombination of these radical species to give a mixture (*c.* 2:1) of the C4-epimeric ketones (131) and (132). In this connection, it should be noted that the formation of the C4-epimeric hydroxy trinitro-

cyclohex-2-enones, (131) and (132), from the phenol (128) is also presumed to occur *via* the radical coupling of the delocalized radical (136) and $^{\bullet}NO_2$; here also the product ratio (131):(132) is *c*. 2:1.

Experimental

Nitration of 2,4-Dimethyl-6-nitrophenol (128)

Fuming nitric acid (d 1.5; 4.5 ml) was added, over 20 minutes, to a stirred solution of the phenol (128) (2g) in dichloromethane at 0^{o}. The resulting pale yellow solution was allowed to warm to 20^{o} and the solvent removed under reduced pressure. The yellow oily solid (*c.* 2.8 g) was shown (^{1}H n.m.r.) to be essentially a mixture of (129)(11%), (130)(36%), (131)(13%), (132)(11%) and (133)(19%). The same sample, after storage for 24h in D_3-acetonitrile at 30^{o}, was shown by ^{1}H n.m.r. spectroscopy to consist of (129)(15%), (130)(37%), (131)(31%) and (132)(16%).

Attempts to isolate all compounds, by fractional crystallization and chromatographic procedures, were not successful. This was due to the instability of the compounds present and difficulty in getting pure material by fractional crystallization. Structural assignments, for those compounds not isolated, are made on the basis of ^{1}H n.m.r. and infrared spectroscopy as well as mass spectral data.

Spectra were obtained for the purest sample of each compound available after fractional recrystallization from dichloromethane/pentane mixtures.

The first compound from fractional crystallization was *c*-6-hydroxy-4,6-dimethyl-2,*r*-4,*c*-5-trinitrocyclohex-2-enone (131) (obtained as a mixture (9:1)(^{1}H n.m.r.) with (129)). ν_{max} (Nujol) 3550, OH; 1737, C=O; 1655, C=C; 1594, 1538, 1320 cm^{-1}, NO_2. ^{1}H n.m.r. (CD_3CN) δ 1.67, s, 3H; 2.18, s, 3H; 5.87, d, $J_{H,H}$ 1.8 Hz, H5; 8.03, d, $J_{H,H}$ 1.8 Hz, H3; ($CDCl_3$) δ 1.67, s, 3H; 5.56, d, $J_{H,H}$ 1.8 Hz, H5; 8.03, d, $J_{H,H}$ 1.8 Hz, H3. (Found: $M^{+\cdot} - HNO_2$ 228.0378. $C_8H_8N_2O_6$ ($M^{+\cdot} - HNO_2$) requires 228.0382.

$M^{+\cdot}$ $-HNO_3$, 212; M^+ - NO,NO_2, 199; M^+ - $2NO_2$, 183).

The next compound isolated was 2,5-dimethyl-3,6-dinitro-1,4-benzoquinone (129), m.p. 177° (dec.) [lit.[96] 175° (dec.)]. ν_{max} (Nujol) 1678, 1674, C=O; 1640, C=C; 1552 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$)δ 2.17, s, Me; (CD_3CN)δ 2.07.

Further recrystallization yielded *c*-6-hydroxy-4,6-dimethyl-2,2,*r*-5-trinitrocyclohex-3-enone (133) (obtained as a mixture (8:2:1) (^1H n.m.r.) with (129) and (132)). ν_{max} (Nujol) 3500, OH; 1760, C=O; 1600, C=C; 1585, 1562, 1350 cm^{-1}, NO_2. ^1H n.m.r. (CD_3CN)δ 1.52, s, Me; 2.20, d, $J_{Me,H}$ 1.8 Hz, Me; 5.58, s, H5; 6.63, q, $J_{H,Me}$ 1.8 Hz, H5. (Found: $M^{+\cdot}$ - HNO_2, 228.0378. $C_8H_8N_2O_6$ (M^+-HNO_2) requires 228.0382. M^+ $-HNO_3$, 212; M^+ - $2NO_2$, 183). On storage in D_3-acetonitrile this compound was shown (^1H n.m.r.) to decompose quantitatively to give a 2:1 mixture of (131) and (132).

The remaining material consisted mainly of 2,5-dimethyl-3-nitro-1,4-benzoquinone (130), m.p. 51.5-52° [lit.[96] 51-52°]. ν_{max} (Nujol) 1673, C=O; 1627, C=C; 1538 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$)δ 2.08, s, Me; 2.14, d, $J_{Me,H}$ 1.5 Hz, Me; 6.75, q, $J_{H,Me}$ 1.5 Hz, H6.

The final compound obtained was *t*-6-hydroxy-4,6-dimethyl-2,*r*-4,-*t*-5-trinitrocyclohex-2-enone (132) obtained in admixture (1:1:2) with (131) and (130)). ^1H n.m.r. (CD_3CN)δ 1.42, s, 3H; 1.98, s, 3H; 5.92, d, $J_{H,H}$ 1.8 Hz, 1H, H5; 7.70, d, $J_{H,H}$ 1.8 Hz, 1H, H3; ($CDCl_3$)δ 1.40, s, 3H; 1.99, s, 3H; 5.90, d, $J_{H,H}$ 2.0 Hz, 1H, H5; 7.53, d, $J_{H,H}$ 2.0 Hz, 1H, H3.

Reaction of 2,4-Dimethyl-6-nitrophenol (128) with Nitrogen Dioxide in Benzene

A solution of the phenol (128) (500 mg) in benzene (5 ml) was deoxygenated with a stream of nitrogen and cooled to 8°. Nitrogen dioxide was bubbled through the stirred suspension for 30s, then stirred under an atmosphere of nitrogen dioxide for a further 2h. The excess nitrogen dioxide was removed in a stream of nitrogen and the solvent removed under reduced pressure. The residue, a pale yellow oily solid (880 mg), was shown (^{1}H n.m.r.) to be a mixture of (129)(12%), (130)(4%), (131)(24%), (132)(12%) and (133)(40%).

APPENDIX II

The data sets used for the X-ray crystal structure analyses contained in this thesis were obtained on two different instruments. For the hydroxy trinitrocyclohex-3-enone (42) (Chapter 2), crystal data, established from precession photographs and measured accurately, by using a Hilger and Watts four circle diffractometer, are presented below. Zr-filtered Cu Kα X-radiation λ(Cu kᾱ)1.5418 Å and the θ/2θ scan technique: were used to collect reflection intensities out to a Bragg angle θ, of 57°. The space group was determined unambiguously as a result of the structure analysis reported below but was initially indicated by systematic absences of appropriate reflections. The cell parameters were determined by least squares refinement, the setting angles of 25 accurately centred reflections ($25^{o} < 2\theta < 35^{o}$) being used.

Crystal data for t-6-hydroxy-2,6-dimethyl-r-2,4,t-5-trinitrocyclohex-3-enone (42) - $C_8H_9N_3O_8$, *M* 275.17, orthorhombic, space group $Pna2_1$, *a* 26.606(3), *b* 6.1685(8), *c* 13.815(2)Å, *U* 2267 $Å^3$, D_m 1.62 gcm^{-3}, D_c 1.61 gcm^{-3}, Z 8, μ(Cu Kᾱ) 12.43 cm^{-1}. The crystal was colourless and of approximate dimensions 0.48 by 0.13 by 0.03 mm. Number of independent reflections measured 1666, number with $I > 3\sigma(I)$1255; maximum Bragg angle θ, 57°; g 0.00000; *R*-factor 0.068; *wR* 0.046; absorption correction, maximum 1.328, minimum 1.062.

Intensity data were processed by means of a Burroughs B6930 computer and programs HILGOUT (based on DRED by J.F. Blount and PICKOUT by R.J. Doedens). Structure solution and

refinement (full matrix least squares) and geometry calculations were carried out on a Prime 750 computer by programs SHELX (G. Sheldrick) and GEOM (S. Motherwell). Diagrams were produced using ORTEP II (C.K. Johnson).

As $Pna2_1$ is a non-centrosymmetric space group direct methods calculations could not be applied directly. Starting phases for some hkO reflections were generated using a centrosymmetric projection down the z axis. Further reflections were phased by tangent refinement processes to define the origin and the enantiomorph. The structure was then solved by using direct methods and difference Fourier syntheses.

For the remaining eight compounds whose structures were determined by X-ray crystal structure analysis (compounds (44), (54), (74), (82), (92), (93), (94) and (96), Chapters 2 and 3), crystal data, established from precession photographs and measured accurately by using a Nicolet XRD P3 four circle diffractometer, are presented below. Molybdenum X-radiation λ(Mo K$\bar{\alpha}$ 0.71069 Å from a graphite crystal monochromator and either the $\theta/2\theta$ or ω scan technique were used to collect reflection intensities out to Bragg angle θ, given below. The space group was in each case, determined unambiguously as a result of the structure analyses reported below but initially indicated by systematic absences of appropriate reflections. The cell parameters were determined, in each case, by least-squares refinement, the setting angles of 25 accurately centred reflections ($20^{\circ} < 2\theta < 30^{\circ}$) being used. Absorption corrections were not applied.

Crystal data for r-2,t-6-dihydroxy-2,6-dimethyl-4,t-5-dinitrocyclohex-3-enone (44) - $C_8H_{10}N_2O_7$, *M* 246.17, monoclinic, space group $P2_1/c$, *a* 5.804(3), *b* 25.47(1), *c* 14.05(2) Å, β 93.84(7)°, *U* 2072Å^3, D_m 1.56 g cm^{-3}, D_c 1.58 g cm^{-3}, *Z* 8, μ(Mo Kᾱ) 1.32 cm^{-1}. The crystal was colourless and of approximate dimensions 0.6 by 0.25 by 0.1 mm. Number of independent reflections measured 2212, number with $I > 3\sigma(I)$ 1965; maximum Bragg angle θ 22.5°; *g* 0.00106; *R*-factor 0.053; *wR* 0.0057. The structure was solved by a translational search in *P*1 of a fragment obtained from the initial Patterson map followed by difference Fourier syntheses.

Crystal data for 4-bromo-t-6-hydroxy-2,6-dimethyl-r-2,t-5-dinitrocyclohex-3-enone (54) - $C_8H_9BrN_2O_6$, *M* 309.06, triclinic, space group $P\bar{1}$, *a* 6.332(2), *b* 8.040(2), *c* 11.188(3) Å, α 97.58(2)°, β 94.58(2)°, γ 95.03(2)°, *U* 560 Å^3, D_m 1.81 g cm^{-3}, D_c 1.83 g cm^{-3}, *Z* 2, μ(Mo Kᾱ) 36.50 cm^{-1}. The crystal was colourless and of approximate dimensions 0.8 by 0.3 by 0.2 mm. Number of independent reflections measured 1850, number with $I > 3\sigma(I)$ 1724; maximum Bragg angle θ 25°; *g* 0.00184; *R*-factor 0.0485; *wR* 0.053. The structure was solved by a translational search to find the bromine atom position and difference Fourier syntheses.

Crystal data for 2,4,5,6-tetramethyl-r-2,t-5,c-6-trinitrocyclohex-3-enone (74) - $C_{10}H_{13}N_3O_7$, *M* 287.24, monoclinic, space group $P2_1/c$, *a* 14.405(2), *b* 7.212(1), *c* 12.271(2) Å, β 94.56(1)°, *U* 1271 Å^3, D_m 1.52 g cm^{-3}, D_c 1.50 g cm^{-3}, *Z* 4, μ(Mo Kᾱ) 1.21 cm^{-1}. The crystal was colourless and of approximate dimensions 0.5 by 0.15 by 0.2 mm. θ/2θ scan

technique. Number of independent reflections measured 1780, number with $I > 3\sigma(I)$ 1300; maximum Bragg angle θ, 24°; g 0.00270; R-factor 0.054; wR 0.058. The structure was solved by direct methods and difference Fourier syntheses.

Crystal data for 2,4,5,6-tetramethyl-r-4,t-5,t-6-trinitrocyclohex-2-enone (82) - $C_{10}H_{13}N_3O_7$, M 287.24, monoclinic, space group $P2_1/n$, a 11.924(3), b 8.491(1), c 13.016(2) Å, β 101.67(2)°, U 1291 Å^3, D_m 1.46 g cm^{-3}, D_c 1.48 g cm^{-3}, Z 4, μ(Mo Kᾱ) 1.19 cm^{-1}. The crystal was colourless and of approximate dimensions 0.8 by 0.5 by 0.3 mm. θ/2θ scan technique. Number of independent reflections measured 2039, number with $I > 3\sigma(I)$ 1446; maximum Bragg angle θ, 24°; g 0.00123; R-factor 0.063 (for 1445 reflections; reflection 101 was subject to interference by the beam stop and was omitted from the final least-squares analysis); wR 0.076. The structure was solved by direct methods and difference Fourier syntheses.

Crystal data for 2,4,6,6-tetramethyl-r-2,t-5-dinitrocyclohex-3-enone (92) - $C_{10}H_{14}N_2O_5$, M 242.22, triclinic space group $P\bar{1}$, a 6.440(1), b 13.919(2), c 14.413(2) Å, α 68.91(1)°, β 85.37(1)°, λ 8807(1)°, U 1201 Å^3, D_m 1.34 g cm^{-3}, D_c 1.33 g cm^{-3}, Z 4, μ(Mo Kᾱ) 1.01 cm^{-1}. The crystal was colourless and of approximate dimensions 0.75 by 0.5 by 0.4 mm. θ/2θ scan technique. Number of independent reflections measured 2846, number with $I > 2\sigma(I)$ 2512; maximum Bragg angle θ, 27.5°; g 0.00200, R-factor 0.052 (for 2510 reflections; reflections 100 and 010 were subject to interference by the beam stop and were omitted from the final least squares

analysis); wR 0.061. The structure was solved by direct methods and difference Fourier syntheses.

Crystal data for 2,4,6,6-tetramethyl-r-4,t-5-dinitrocyclohex-2-enone (93) - $C_{10}H_{14}N_2O_5$, M 242.24, monoclinic, space group Pc, a 11.549(4), b 6.705(2), c 15.376(9) Å, β 90.32(4)°, U 1191 Å^3, D_m 1.33 g cm^{-3}, D_c 1.35 g cm^{-3}, Z 4, μ(Mo K$\bar{\alpha}$) 1.02 cm^{-1}. The crystal was colourless and of approximate dimensions 0.6 by 0.5 by 0.4 mm. ω scan technique. Number of independent reflections measured 1592, number with $I > 1.5\sigma(I)$ 1252; maximum Bragg angle θ 24°; g 0.00112; R-factor 0.076; wR 0.071. The structure was solved by direct methods and difference Fourier syntheses.

Crystal data for r-2-hydroxy-2,4,6,6-tetramethyl-t-5-nitrocyclohex-3-enone (94) - $C_{10}H_{15}NO_4$, M 213.23, triclinic, space group $P\bar{1}$, a 6.580(1), b 7.324(1), c 12.169(2) Å, α 82.70(2)°, β 88.00(2)°, γ 74.19(2)°, U 560 Å^3, D_m 1.24 g cm^{-3}, D_c 1.26 g cm^{-3}, Z 2, μ(Mo K$\bar{\alpha}$) 0.91 cm^{-1}. The crystal was colourless and of approximate dimensions 0.6 by 0.4 by 0.35 mm. ω scan technique. Number of independent reflections measured 1561, number with $I > 2\sigma(I)$ 963; maximum Bragg angle θ 25°; g 0.00203; R-factor 0.064 (for 962 reflections; reflection 001 was subject to interference by the beam stop and was omitted from the final least squares analysis); wR 0.073. The structure was solved by direct methods and difference Fourier syntheses.

Crystal data for c-6-hydroxy-2,4,5,6-tetramethyl-r-2,c-5-dinitrocyclohex-3-enone (96) - $C_{10}H_{14}N_2O_6$, M 258.24, monoclinic,

space group $P2_1/c$, a 12.715(4), b 8.620(2), c 10.784(3) Å, β 93.05(3)°, U 1180 Å^3, D_c 1.45 g cm^{-3}, Z 4, μ(Mo Kᾱ) 1.14 cm^{-1}. The crystal was colourless and of approximate dimensions 0.6 by 0.45 by 0.3 mm. θ/2θ scan technique. Number of independent reflections measured 1758, number with $I > 2\sigma(I)$ 1437; maximum Bragg angle θ 25°; g 0.00088; R-factor 0.059; wR 0.068. The structure was solved by direct methods and difference Fourier syntheses.

Intensity data were processed and structure solution and refinement (blocked cascade least-squares, and geometry calculations were carried out using a Data General Nova 4X computer and SHELXTL[97] (G. Sheldrick) system of programs (designed specifically for minicomputer use). Diagrams were produced using the SHELXTL graphics programme XP and a Tektronix 4113A colour graphics unit and Tektronix 4662 plotter.

Least-squares refinements were employed by using reflection weights $1/\sigma^2(F)+g(F^2)$. The function minimised was $\Sigma w(|Fo|-|Fc|)^2$. Anomalous dispersion corrections were from Cromer and Libermann[98]. Methyl and methylene hydrogens were included as rigid groups pivoting about their carbon atoms and all non-hydrogen atoms were assigned anisotropic thermal parameters. The hydroxy group hydrogen atoms for compounds (94) and (96) were found by difference Fourier calculations, but their positions were not refined. Final Fourier syntheses show no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.

Further, more comprehensive material regarding the structural information for the abovementioned structures (temperature factors, structure factor amplitudes, interatomic distances, bond angles and torsional angles) is deposited with the Editor-in-Chief, Editorial and Publications Service,

CSIRO, 314 Albert St., East Melbourne, Victoria 3002,
Australia.

TABLE 1. Fractional coordinates for non-hydrogen atoms in *t*-6-hydroxy-2,6-dimethyl-*r*-2,4,*t*-5-trinitrocyclohex-3-enone (42), $C_8H_9N_3O_8$.

Molecule 1

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3U*
C(1)	2875(3)	10174(14)	5247( )	29(3)
C(2)	3145(4)	9586(17)	6261(7)	47(4)
C(3)	3566(3)	8058(15)	6131(7)	33(4)
C(4)	3760(3)	7670(14)	5298(8)	26(3)
C(5)	3573(3)	8293(16)	4330(8)	43(4)
C(6)	3806(3)	8784(16)	4389(7)	33(4)
C(7)	3259(3)	11603(16)	6824(7)	73(5)
C(8)	2725(3)	6587(15)	4452(7)	60(4)
N(2)	2732(3)	8389(14)	6833(5)	59(3)
N(4)	4222(2)	6292(11)	5267(5)	39(3)
N(5)	3816(3)	10576(13)	4077(5)	51(3)
O(1)	2552(2)	11496(10)	5250(5)	59(3)
O(6)	2869(2)	9839(11)	3511(5)	71(3)
O(21)	2742(3)	6435(11)	6838(6)	99(3)
O(22)	2432(2)	9426(14)	7287(6)	112(4)
O(41)	4348(2)	5424(12)	6013(5)	68(3)
O(42)	4432(2)	6102(11)	4455(5)	62(3)
O(51)	4089(2)	10675(12)	3394(5)	71(3)
O(52)	3699(2)	12157(10)	4588(4)	68(3)

* For anisotropic atoms, the equivalent isotropic temperature factor (U) is defined as one-third of the trace of the orthoganolised U_{11} tensor.

TABLE 1 (cont.)

Molecule 2

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3U
C*(1)	3753(3)	4756(15)	10612(7)	41(4)
C*(2)	4066(3)	5263(16)	9712(7)	42(4)
C*(3)	4503(3)	6769(15)	9916(7)	37(4)
C*(4)	4634(3)	7195(14)	10801(8)	41(4)
C*(5)	4393(3)	6468(15)	11735(6)	34(3)
C*(6)	3831(3)	6051(16)	11508(7)	42(4)
C*(7)	4251(3)	3159(15)	9210(5)	54(4)
C*(8)	3565(3)	8336(13)	11355(6)	41(4)
N*(2)	3714(4)	6492(18)	8985(7)	65(4)
N*(4)	5098(2)	8676(11)	10954(6)	47(3)
N*(5)	4628(2)	4252(12)	11994(5)	46(3)
O*(1)	3435(2)	3400(9)	10576(4)	58(3)
O*(6)	3637(2)	5069(11)	12345(4)	54(3)
O*(21)	3780(4)	8334(14)	8813(8)	135(5)
O*(22)	3385(3)	5325(14)	8612(7)	114(5)
O*(41)	5266(2)	9557(11)	10226(6)	67(3)
O*(42)	5261(2)	8772(11)	11785(6)	73(3)
O*(51)	4877(2)	4289(12)	12724(5)	76(3)
O*(51)	4526(2)	2784(10)	11458(5)	61(3)

TABLE 2. Fractional coordinates for atoms in *r*-2,*t*-6-dihydroxy-2,6-dimethyl-4,*t*-5-dinitrocyclohex-3-enone (44), $C_8H_{10}N_2O_7$.

Molecule 1

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	-1882(7)	-475	2406(3)	27(1)
C(2)	-1165(8)	-221(2)	3369(3)	30(2)
C(3)	181(7)	272(2)	3255(3)	27(1)
C(4)	424(7)	499(2)	2427(3)	25(1)
C(5)	-572(7)	298(2)	1499(3)	26(1)
C(6)	-766(7)	-303(2)	1522(3)	27(1)
C(7)	-3227(8)	-122(2)	3946(4)	38(2)
C(8)	1640(8)	-546(2)	1551(4)	36(2)
N(4)	1655(6)	1002(1)	2402(3)	28(1)
N(5)	-3017(6)	512(1)	1312(3)	29(1)
O(1)	-3199(5)	-840(1)	2380(3)	40(1)
O(2)	443(6)	-580(1)	3874(3)	45(1)
O(6)	-2087(5)	-441(1)	684(2)	34(1)
O(41)	1495(5)	1246(1)	1654(2)	38(1)
O(42)	2723(5)	1150(1)	3132(2)	42(1)
O(51)	-4411(5)	379(1)	1879(2)	35(1)
O(52)	-3429(6)	793(1)	627(3)	44(1)
H(3)	911(7)	432(2)	3816(3)	-
H(5)	408(7)	405(2)	1010(3)	-

TABLE 2 (cont.)

Molecule 2

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1')	3870(7)	3016(2)	4377(3)	20(1)
C(2')	4151(7)	2866(2)	3340(3)	24(1)
C(3')	5399(7)	2358(2)	3249(3)	24(1)
C(4')	5891(7)	2038(2)	3966(3)	21(1)
C(5')	5298(7)	2127(2)	4964(3)	23(1)
C(6')	5198(7)	2718(2)	5171(3)	24(1)
C(7')	1802(7)	2852(2)	2790(3)	31(2)
C(8')	7648(8)	2936(2)	5264(4)	35(2)
N(4')	7059(6)	1541(1)	3774(3)	28(1)
N(5')	2934(6)	1889(1)	5090(3)	27(1)
O(1')	2720(5)	3393(1)	4578(2)	28(1)
O(2')	5676(5)	3250(1)	2957(2)	33(1)
O(6')	4093(5)	2780(1)	6029(2)	31(1)
O(4')	7254(6)	1220(1)	4420(2)	40(1)
O(42')	7733(5)	1480(1)	2976(2)	41(1)
O(51')	1277(5)	2085(1)	4637(2)	35(1)
O(52')	2821(6)	1523(1)	5631(3)	46(1)
H(3')	5866(7)	2259(2)	2631(3)	-
H(5')	6448(7)	1965(2)	5391(3)	-

TABLE 3. Fractional coordinates for atoms in 4-bromo-*t*-6-hydroxy-2,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (54), $C_8H_9BrN_2O_6$.

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
Br	2616(1)	8349(1)	5625(1)	53(1)
C(1)	2975(5)	6865(4)	1404(3)	31(1)
C(2)	2194(5)	8573(4)	1868(3)	31(1)
C(3)	1999(5)	8850(4)	3198(3)	31(1)
C(4)	2711(5)	7842(4)	3943(3)	31(1)
C(5)	3760(5)	6290(4)	3539(3)	32(1)
C(6)	2977(6)	5518(4)	2240(3)	34(1)
C(7)	3599(7)	10017(5)	1473(4)	44(1)
C(8)	727(7)	4650(5)	2235(4)	48(1)
N(2)	-58(5)	8638(4)	1252(3)	41(1)
N(5)	6130(5)	6786(4)	3625(3)	39(1)
O(1)	3576(5)	6625(4)	408(2)	48(1)
O(6)	4389(5)	4323(3)	1868(3)	48(1)
O(21)	-914(5)	7384(5)	629(3)	64(1)
O(22)	-831(5)	9964(4)	1437(3)	62(1)
O(51)	6784(4)	7626(4)	2874(3)	46(1)
O(52)	7244(5)	6351(5)	4432(3)	69(1)
H(3)	1323(6)	9809(4)	3528(3)	-
H(5)	3413(5)	5454(4)	4049(3)	-

TABLE 4. Selected torsion angles for cyclohex-3-enones (42), (44) and (54)

Atoms	Angles				
	42[A]	42[B]	44[A]	44[B]	54
C(4)-C(3)-C(2)-C(1)	15.7	12.3	9.0(7)	9.6(6)	9.1(5)
C(3)-C(4)-C(5)-C(6)	-20.0	-26.9	-28.8(6)	-28.1(6)	-28.6(5)

[A] Molecule 1.

[B] Molecule 2.

TABLE 6. Fractional coordinates for atoms in 2,4,5,6-tetramethyl-*r*-2,*t*-5,*c*-6-trinitrocyclohex-3-enone (74), $C_{10}H_{13}N_3O_7$.

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	7520(2)	7573(4)	4568(3)	39(1)
C(2)	6491(2)	7274(4)	4388(2)	37(1)
C(3)	6335(2)	5860(4)	3533(3)	36(1)
C(4)	6967(2)	4760(4)	3030(2)	37(1)
C(5)	7991(2)	4854(4)	3253(2)	37(1)
C(6)	8278(2)	6775(4)	3727(3)	37(1)
C(7)	5940(3)	6851(6)	5482(3)	56(1)
C(8)	6690(3)	3315(5)	2244(3)	50(1)
C(9)	8644(2)	4196(5)	2299(3)	51(1)
C(10)	9233(2)	6788(6)	4212(3)	55(1)
N(2)	6095(2)	9168(4)	4030(2)	47(1)
N(5)	8100(2)	3502(4)	4237(3)	51(1)
N(6)	8334(2)	8137(4)	2754(3)	41(4)
O(1)	7754(2)	8368(4)	5356(2)	59(1)
O(21)	3706(2)	9455(4)	5475(2)	75(1)
O(22)	5585(2)	9172(4)	3284(3)	76(1)
O(51)	7704(2)	3958(4)	5107(2)	67(1)
O(52)	8568(2)	2115(4)	4088(3)	85(1)
O(61)	7626(2)	8940(3)	2567(2)	55(1)
O(62)	9071(2)	8353(4)	2224(2)	70(1)

TABLE 7. Fractional coordinates for atoms in 2,4,5,6-tetramethyl-*r*-4,*t*-5,*t*-6-trinitrocyclohex-2-enone (82), $C_{10}H_{13}N_3O_7$.

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	684(3)	6237(4)	6487(3)	47(1)
C(2)	877(3)	7876(5)	6227(3)	48(1)
C(3)	685(3)	9042(4)	6847(3)	45(1)
C(4)	357(3)	8880(4)	7895(3)	38(1)
C(5)	218(3)	7108(4)	8247(3)	45(1)
C(6)	-122(3)	6045(4)	7274(3)	48(1)
C(7)	1332(4)	8143(6)	5250(3)	73(2)
C(8)	1199(3)	9829(4)	8714(3)	56(1)
C(9)	-581(4)	6905(5)	9011(3)	69(2)
C(10)	-1321(3)	6291(6)	6656(4)	65(2)
N(4)	-795(3)	9759(4)	7831(3)	53(1)
N(5)	1440(3)	6690(4)	8812(3)	61(1)
N(6)	-7(4)	4307(4)	7636(3)	81(2)
O(1)	982(2)	5123(3)	6049(2)	71(1)
O(41)	-1415(2)	9930(3)	6973(2)	66(1)
O(42)	-1019(3)	10273(4)	8640(3)	85(1)
O(51)	1633(3)	6562(4)	9758(2)	94(1)
O(52)	2160(2)	6551(4)	8273(2)	73(1)
O(61)	754(4)	3939(4)	8359(3)	127(2)
O(62)	-725(5)	3397(5)	7204(4)	146(2)

TABLE 8. Fractional coordinates for atoms in 2,4,6,6-tetramethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (92), $C_{10}H_{14}N_2O_5$.

Molecule 1

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	2551(4)	4038(2)	2895(2)	45(1)
C(2)	2204(4)	4854(2)	3404(2)	42(1)
C(3)	799(4)	5714(2)	2887(2)	44(1)
C(4)	181(4)	5917(2)	1983(2)	43(1)
C(5)	787(4)	5208(2)	1421(2)	45(1)
C(6)	1171(4)	4084(2)	2087(2)	43(1)
C(7)	4273(4)	5235(3)	3570(2)	66(1)
C(8)	-1080(5)	6848(2)	1448(2)	62(1)
C(9)	2091(5)	3455(2)	1469(2)	62(1)
C(10)	-947(4)	3631(2)	2585(2)	55(1)
N(2)	1132(4)	4238(2)	444(2)	54(1)
N(5)	2736(4)	5633(7)	752(2)	60(1)
O(1)	3831(3)	3375(2)	3203(2)	71(7)
O(21)	-755(3)	4266(2)	4546(1)	66(1)
O(22)	2236(4)	3762(2)	5098(2)	98(1)
O(51)	4363(3)	5557(2)	1147(2)	81(1)
O(52)	2578(4)	6030(2)	-135(2)	103(1)
H(3)	297(4)	6156(2)	3237(2)	-
H(5)	-374(4)	5190(2)	1050(2)	-

TABLE 8 (cont.)

Molecule 2

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(11)	2413(4)	-1159(2)	2789(2)	51(1)
C(12)	2857(4)	-357(2)	1727(2)	48(1)
C(13)	4319(4)	472(2)	1668(2)	44(1)
C(14)	4943(4)	644(2)	2445(2)	42(1)
C(15)	4270(4)	-45(2)	3488(2)	45(1)
C(16)	3771(4)	-1152(2)	3603(2)	49(1)
C(17)	822(5)	74(3)	1262(2)	75(1)
C(18)	6309(4)	1529(2)	2351(2)	58(1)
C(19)	5864(5)	-1669(2)	3457(2)	66(1)
C(20)	2729(6)	-1759(3)	4638(2)	78(1)
N(12)	3896(4)	-981(2)	1115(2)	64(1)
N(15)	2387(4)	446(2)	3836(2)	61(1)
O(11)	1093(4)	-1796(2)	2929(2)	85(1)
O(121)	5765(3)	-945(2)	950(2)	76(1)
O(122)	2788(5)	-1443(3)	789(3)	129(2)
O(151)	2557(4)	788(2)	4493(2)	95(1)
O(152)	787(4)	474(2)	3443(2)	93(1)
H(13)	4849(4)	914(2)	1018(2)	-
H(15)	5425(4)	-107(2)	3887(2)	-

TABLE 9. Fractional coordinates for atoms in 2,4,6,6-tetramethyl-*r*-4,*t*-5-dinitrocyclohex-2-enone (93), $C_{10}H_{14}N_2O_5$.

Molecule 1

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	3917(8)	5863(14)	-438(6)	38(3)
C(2)	4590(7)	4468(14)	106(6)	38(3)
C(3)	4331(7)	4108(13)	939(6)	36(3)
C(4)	3295(7)	4963(12)	1378(6)	33(3)
C(5)	2460(7)	6074(13)	753(6)	38(3)
C(6)	3048(8)	7208(13)	-11(6)	36(3)
C(7)	5614(8)	3439(16)	-332(6)	60(4)
C(8)	2677(8)	3380(16)	1934(6)	53(4)
C(9)	2144(9)	7960(16)	-628(6)	59(4)
C(10)	3723(9)	8984(14)	344(7)	58(4)
N(4)	3728(6)	6527(12)	2041(5)	49(3)
N(5)	1599(6)	4583(12)	372(5)	49(3)
O(1)	4118(6)	6027(11)	-1202(4)	61(3)
O(41)	3015(7)	7558(12)	2406(5)	80(3)
O(42)	4758(6)	6571(11)	2209(4)	66(3)
O(51)	1981(6)	3333(11)	-125(4)	67(3)
O(52)	589(5)	4749(12)	597(5)	79(3)
H(3)	4838(7)	3259(13)	1270(6)	-
H(5)	2086(7)	7078(13)	1097(6)	-

TABLE 9 (cont.)

Molecule 2

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(11)	7101(7)	9315(13)	1827(6)	40(3)
C(12)	7109(8)	9764(14)	2785(6)	42(3)
C(13)	7935(8)	9077(17)	3269(6)	58(4)
C(14)	9028(8)	8114(14)	2949(6)	41(3)
C(15)	9144(7)	8012(13)	1958(5)	36(3)
C(16)	7974(9)	7835(15)	1461(6)	48(3)
C(17)	6101(9)	10960(17)	3107(7)	66(4)
C(18)	10092(8)	9051(18)	3396(7)	75(5)
C(19)	8145(11)	8047(20)	484(6)	85(5)
C(20)	7470(8)	5733(14)	1634(8)	63(4)
N(14)	9082(8)	5885(14)	3270(6)	63(3)
N(15)	9710(7)	9920(14)	1683(6)	61(4)
O(11)	6397(6)	10132(11)	1332(5)	74(3)
O(141)	9863(8)	4850(12)	3024(6)	81(3)
O(142)	8362(8)	5361(15)	3709(6)	112(4)
O(151)	9198(7)	11454(11)	1724(5)	77(3)
O(152)	10688(6)	9763(11)	1376(6)	92(4)
H(13)	7841(9)	9184(17)	3887(6)	-
H(15)	9579(7)	6836(13)	1819(6)	-

TABLE 10. Fractional coordinates for atoms in *r*-2-hydroxy-2,4,6,6-tetramethyl-*t*-5-nitrocyclohex-3-enone (94), $C_{10}H_{15}NO_4$.

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	1750(7)	9782(7)	3211(4)	46(2)
C(2)	2458(8)	7782(7)	3855(4)	47(2)
C(3)	4296(8)	6488(7)	3336(4)	51(2)
C(4)	5042(7)	6832(7)	2334(4)	44(2)
C(5)	4120(7)	8702(7)	1640(4)	42(2)
C(6)	3154(7)	10372(7)	2295(3)	42(2)
C(7)	637(9)	6877(9)	4004(5)	74(3)
C(8)	6826(8)	5419(7)	1823(4)	62(2)
C(9)	1978(9)	12158(7)	1562(4)	64(2)
C(10)	4983(8)	10787(7)	2895(4)	61(2)
N(5)	2475(6)	8397(6)	893(3)	55(2)
O(1)	152(6)	10907(5)	3594(3)	65(2)
O(2)	3201(6)	8005(6)	4911(3)	67(2)
O(51)	814(6)	8278(6)	1303(3)	79(2)
O(52)	2918(7)	8285(7)	-69(3)	95(2)
H(2)	2069	8448	5312	-
H(3)	4993(8)	5306(7)	3769(4)	-
H(5)	5250(7)	9065(7)	1229(4)	-

TABLE 11. Fractional coordinates for atoms in *c*-6-hydroxy-2,4,5,6-tetramethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (96), $C_{10}H_{14}N_2O_6$.

Atom	10^4 X/a	10^4 Y/b	10^4 Z/c	10^3 U
C(1)	8579(2)	4615(4)	1780(3)	33(1)
C(2)	8059(2)	3860(4)	2952(3)	39(1)
C(3)	6944(2)	4398(4)	3194(3)	39(1)
C(4)	6442(2)	5441(4)	2558(3)	37(1)
C(5)	6959(2)	6211(4)	1411(3)	40(1)
C(6)	8174(2)	6204(4)	1430(3)	35(1)
C(7)	8729(3)	4140(4)	4064(3)	52(1)
C(8)	5334(3)	5916(5)	2925(4)	55(1)
C(9)	6535(3)	7801(4)	1156(4)	62(1)
C(10)	8529(3)	7400(4)	2367(3)	47(1)
N(2)	8051(2)	2109(3)	2677(3)	52(1)
N(5)	6695(2)	5146(4)	297(3)	57(1)
O(1)	9313(2)	4030(3)	1216(2)	48(1)
O(21)	7277(2)	1569(3)	2235(3)	71(1)
O(22)	8830(2)	1368(3)	2884(4)	90(1)
O(51)	7073(3)	3845(3)	289(2)	73(1)
O(52)	6156(3)	5652(4)	-495(3)	104(1)
O(6)	8590(2)	6610(3)	229(2)	52(1)
H(3)	6597(2)	3923(4)	3867(3)	-
H(6)	9216	5952	5	-

TABLE 12. Selected torsion angles for cyclohex-3-enones (74), (92), (94) and (96).

Atoms	Angles (degrees)				
	(74)[A]	(92)(molecule 1)	(92)(molecule 2)	(94)	(96)
C(4)-C(3)-C(2)-C(1)	-7.6(5)	-12.6(3)	-11.2(4)	-12.0(8)	3.2(4)
C(3)-C(4)-C(5)-C(6)	23.1(4)	27.4(3)	27.4(3)	27.5(7)	25.2(4)
C(3)-C(4)-C(5)-N(5)	-86.8(4)	-94.9(2)	-95.4(3)	-95.4(6)	-86.0(3)

[A] For the enantiomer of Fig.1.

[B] For the enantiomer of Fig.6.

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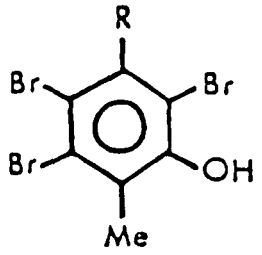
BLOCK B.



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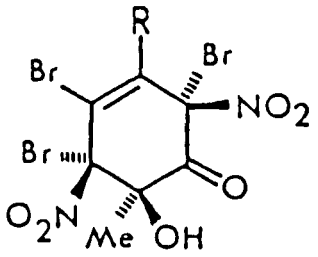
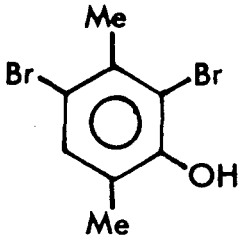
(4) R=Me



(9) R=Br
(7) R=Me



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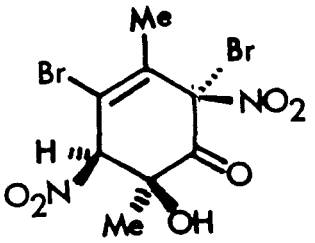
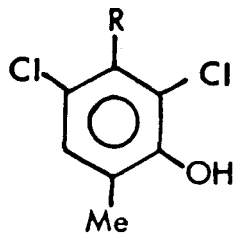
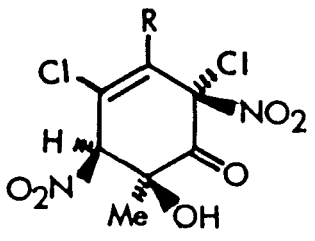


(21)

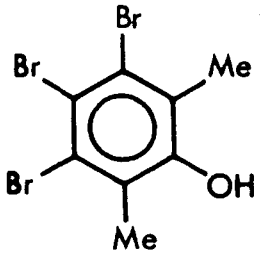


(22) (a) R=H
(b) R=Cl



(23) (a) R=H
(b) R=Cl

BLOCK C.



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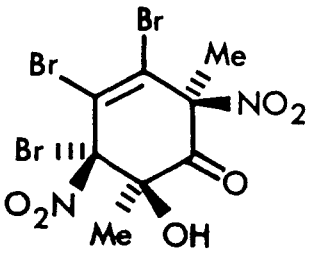
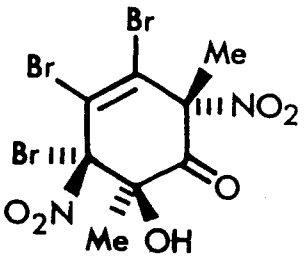


(25)



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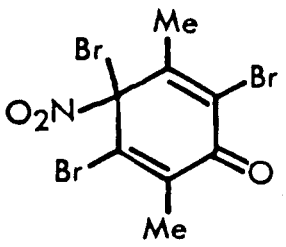

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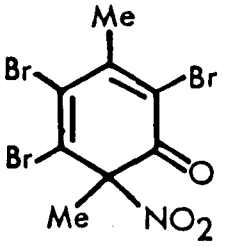
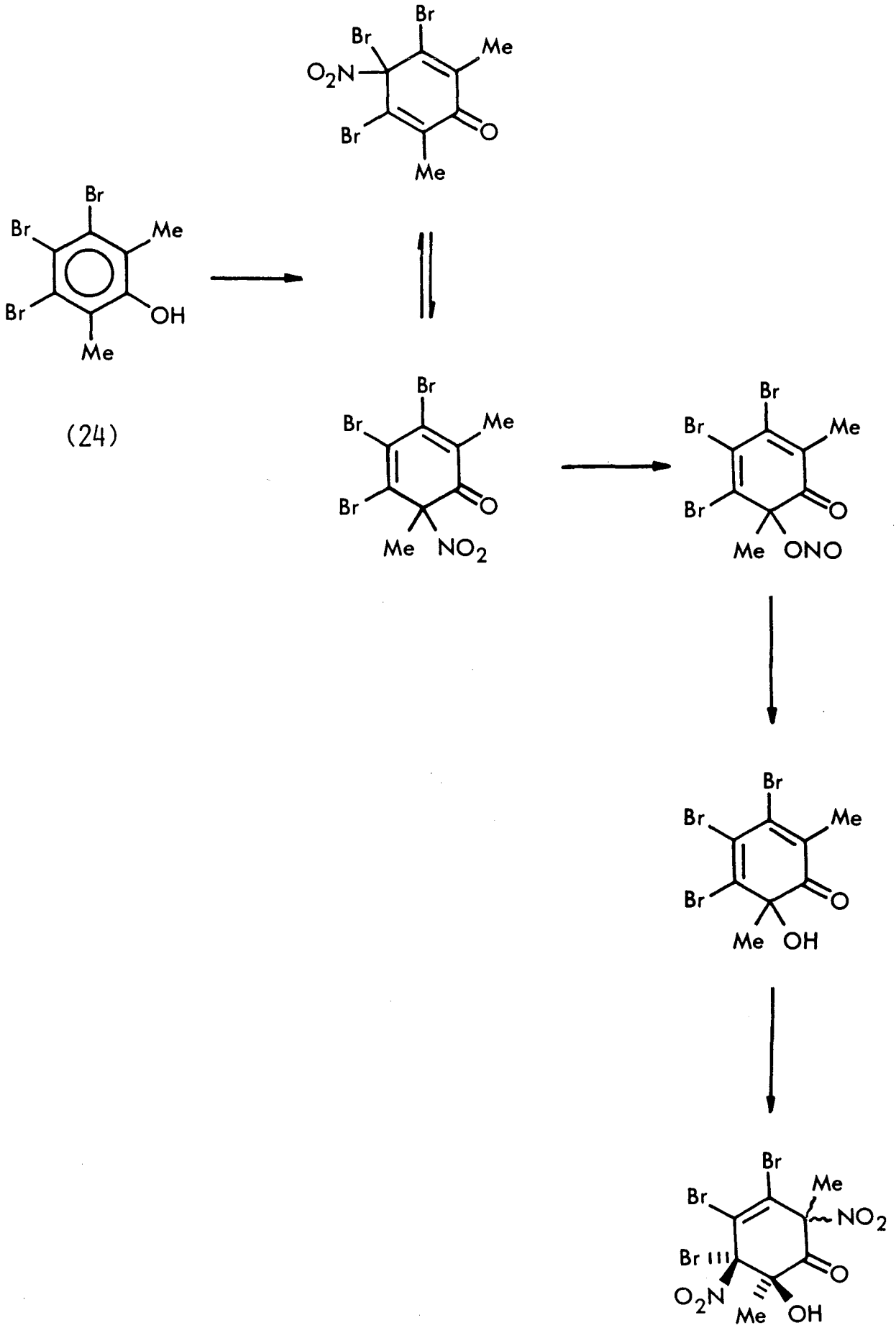
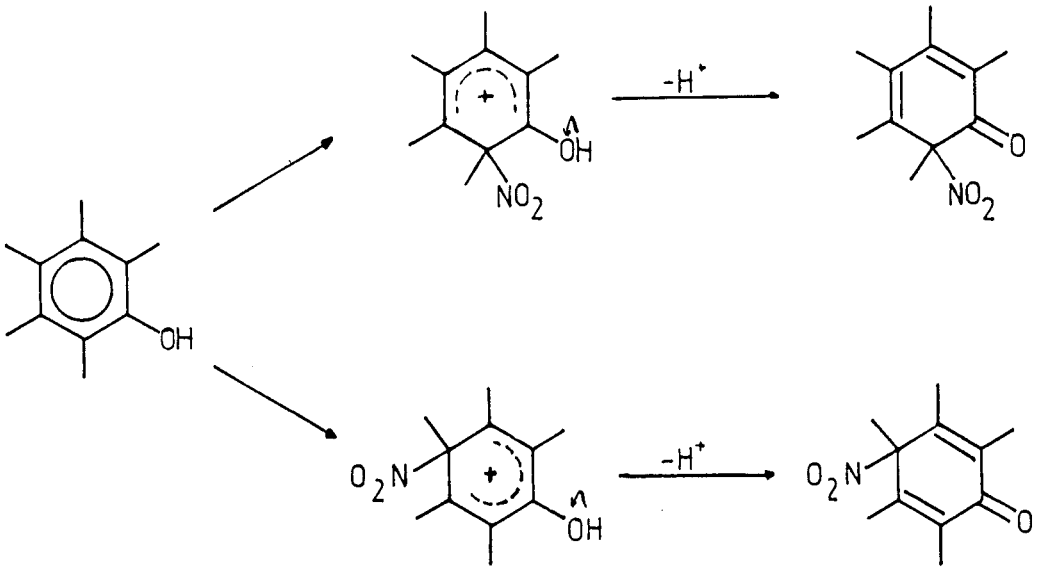


(11B)



SCHEME 9.

(25), (26)



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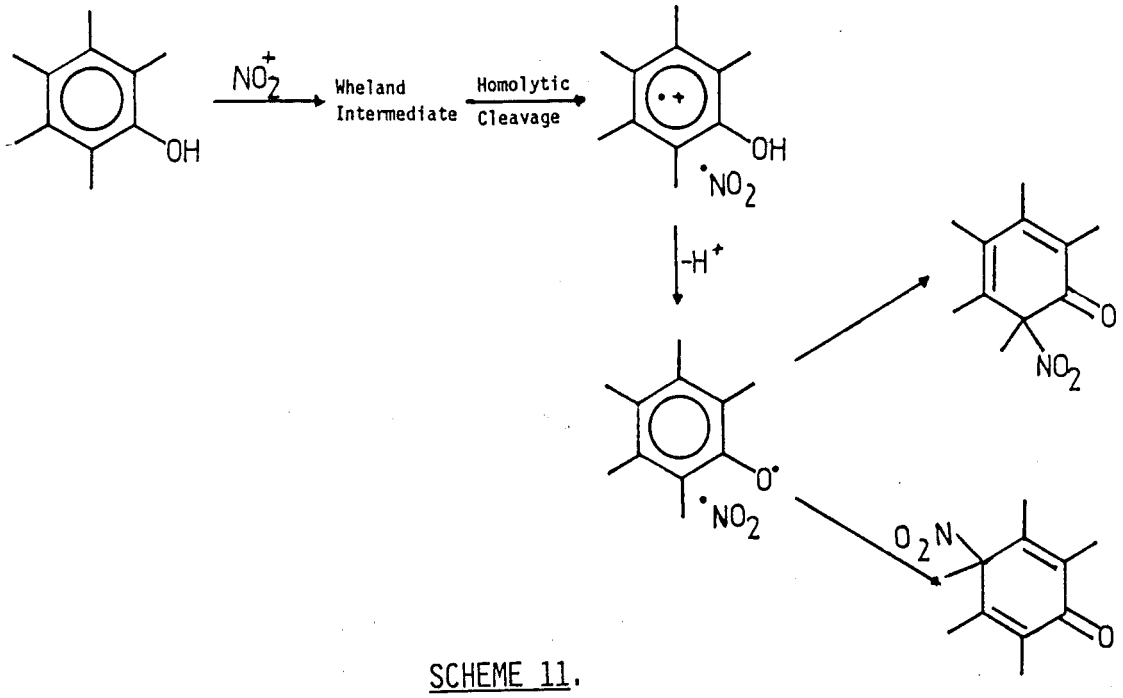

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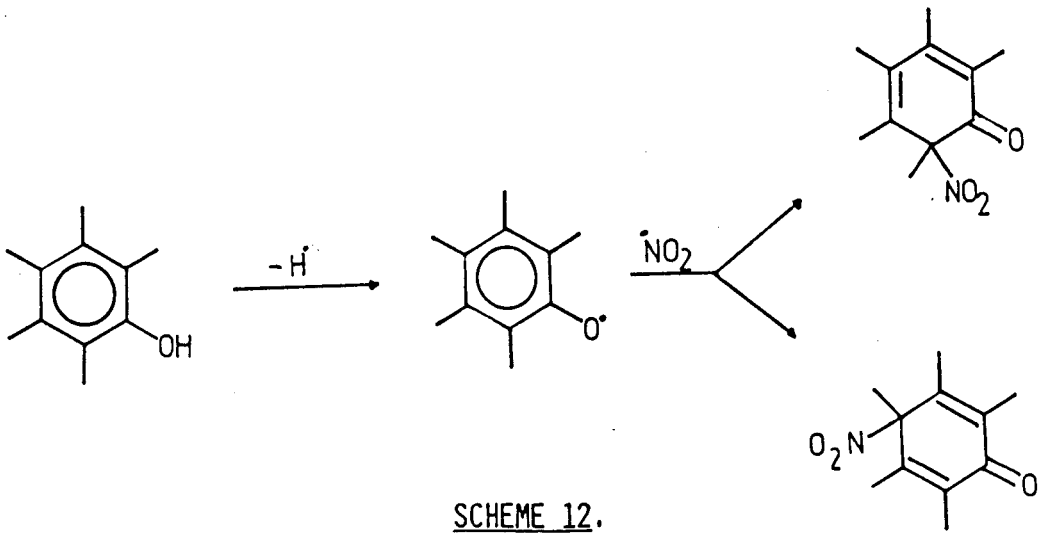

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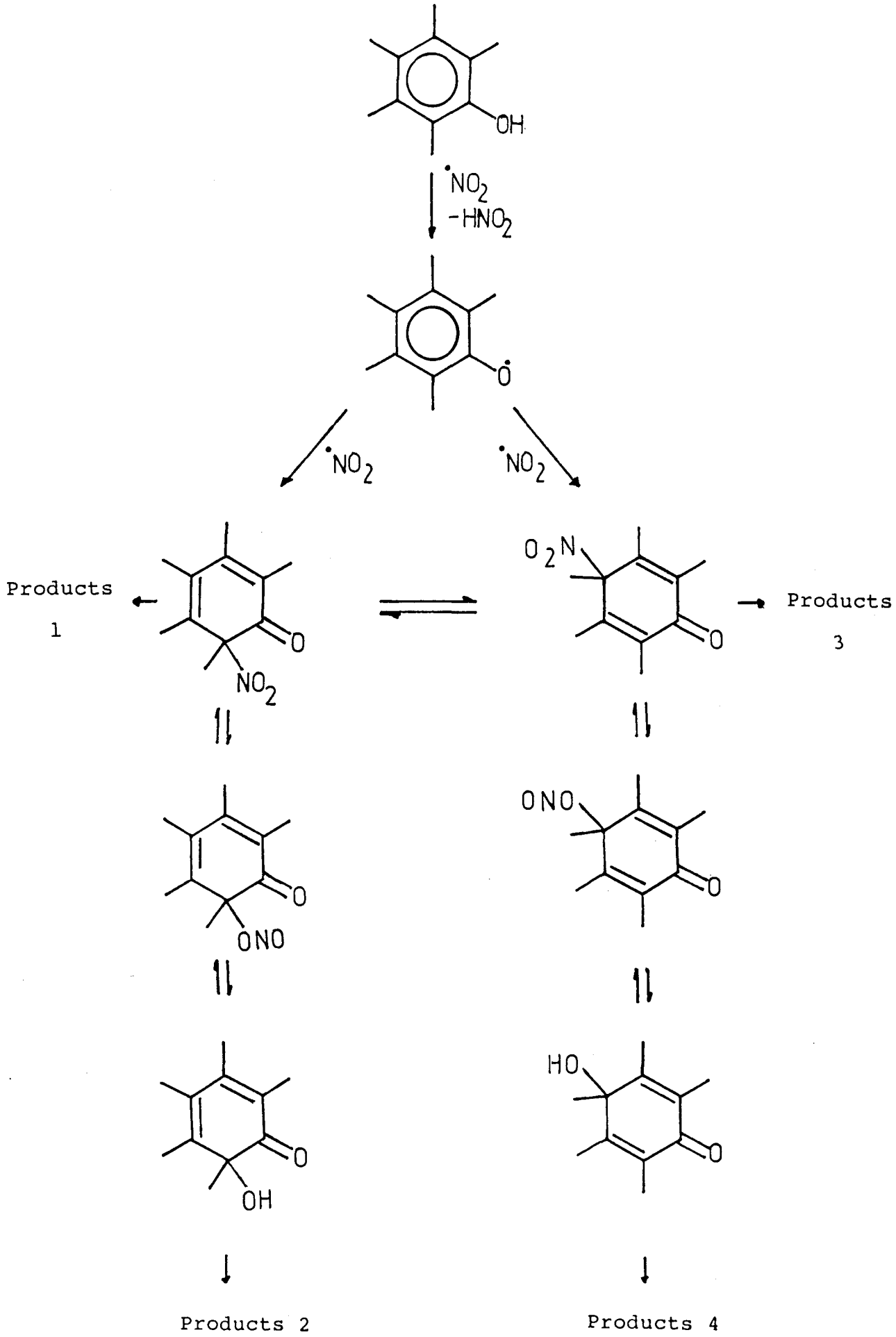
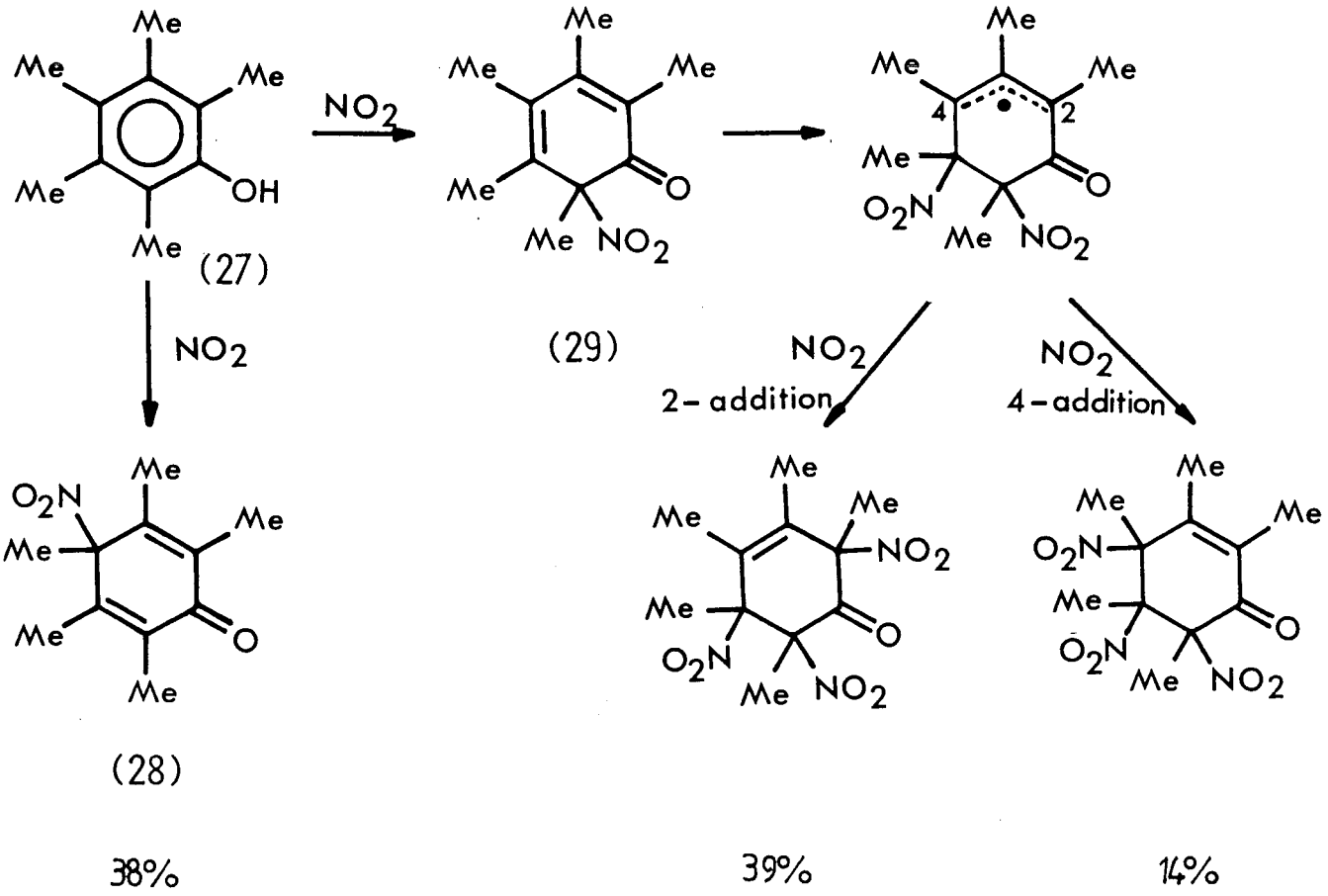

OH
$^{\bullet}NO_2$
$-HNO_2$
O
$^{\bullet}NO_2$
$^{\bullet}NO_2$
Products
1
O
NO_2
O_2N
O
Products
3
O
ONO
ONO
O
HO
O
OH
Products 2
Products 4

SCHEME 13.



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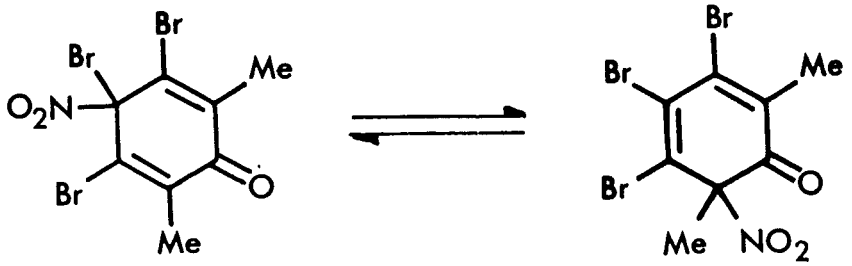
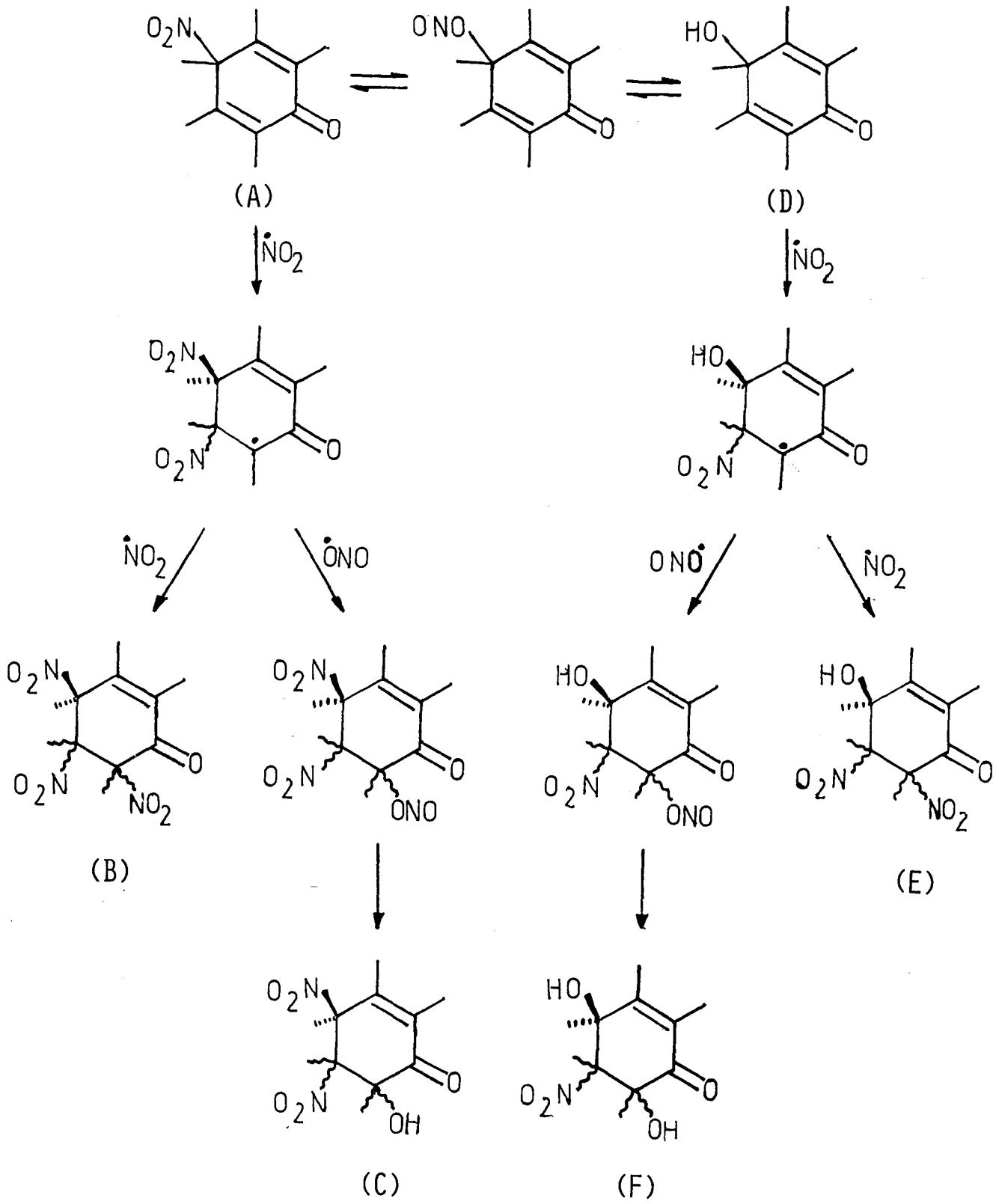
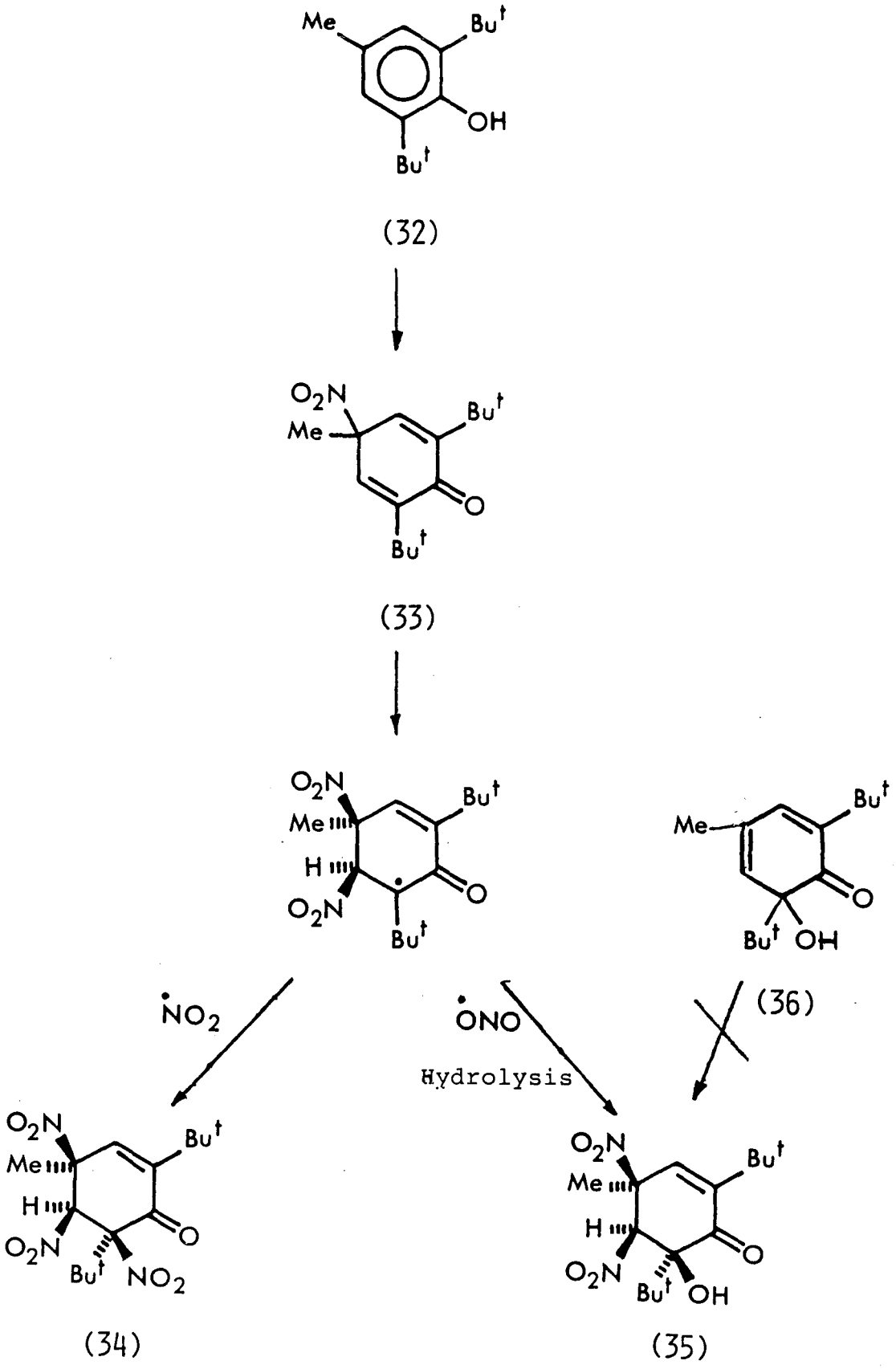


(30) (31)

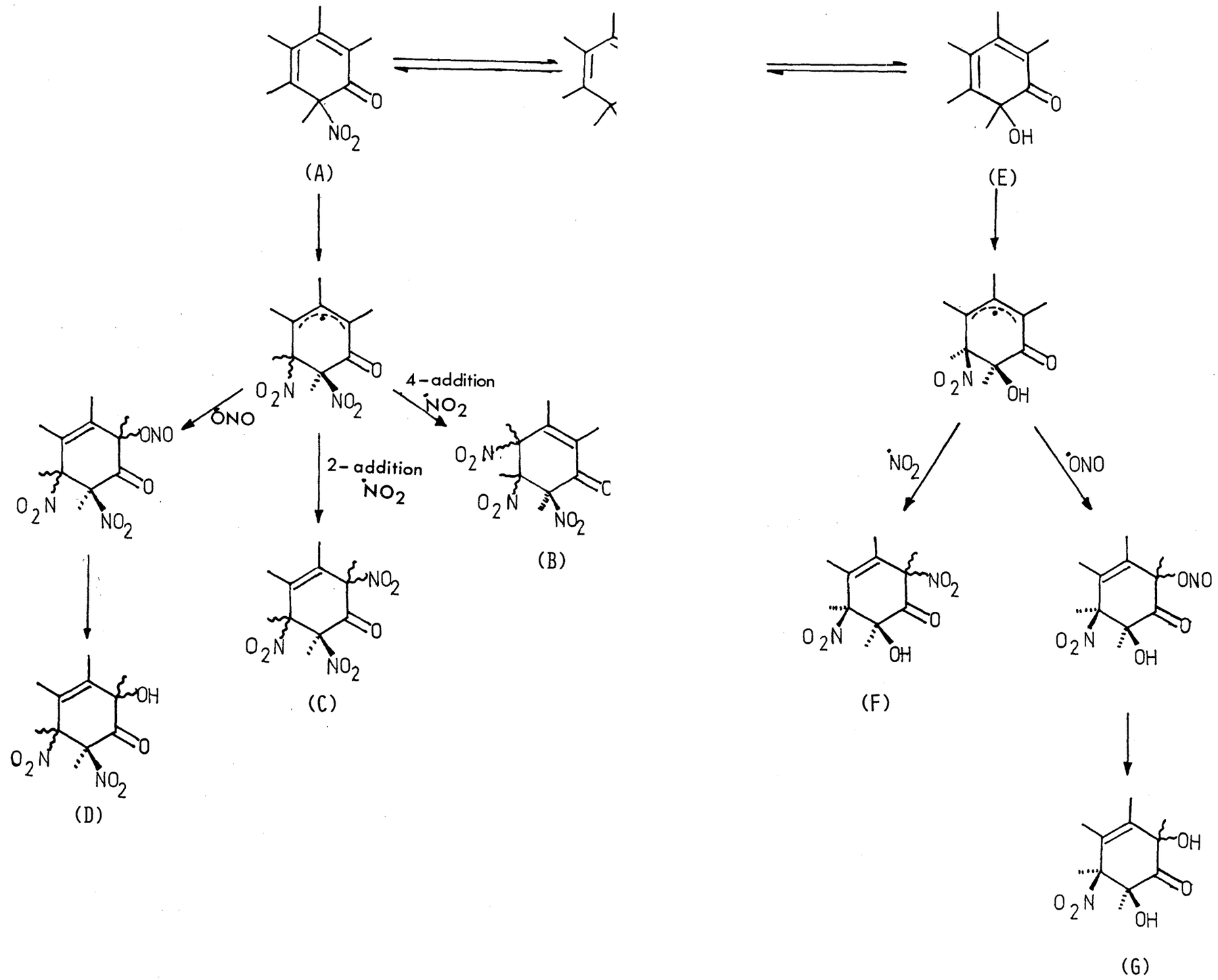
SCHEME 15.



SCHEME 16.


Me
Bu^t
OH
Bu^t
(32)
O_2N
Me
Bu^t
O
Bu^t
(33)
O_2N
Me
H
O_2N
Bu^t
O
Bu^t
Me
Bu^t
O
Bu^t OH
(36)
$\dot{N}O_2$
$\dot{O}NO$
Hydrolysis
O_2N
Me
H
O_2N
Bu^t
O
Bu^t
NO_2
(34)
O_2N
Me
H
O_2N
Bu^t
O
Bu^t OH
(35)

SCHEME 17.



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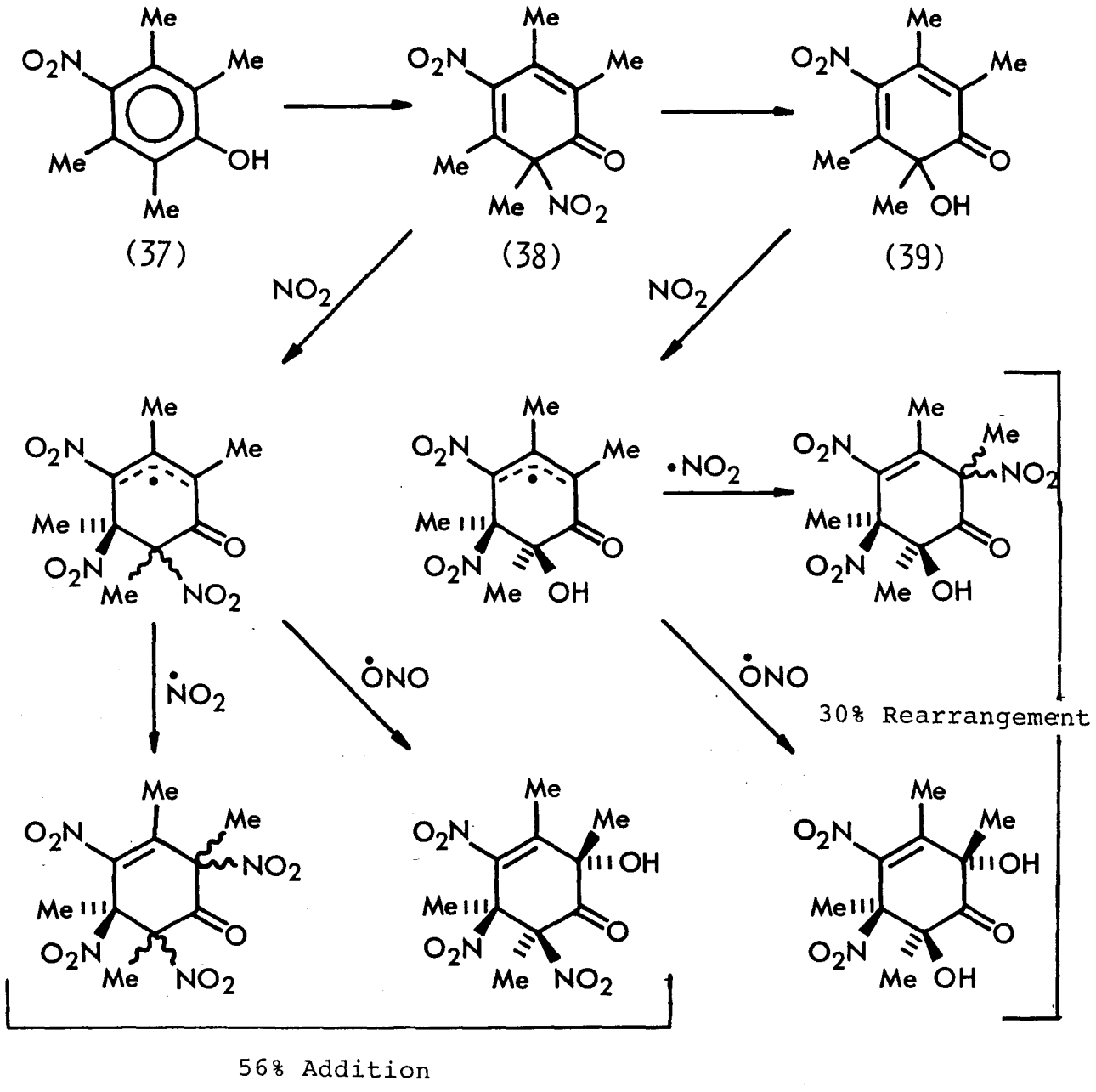
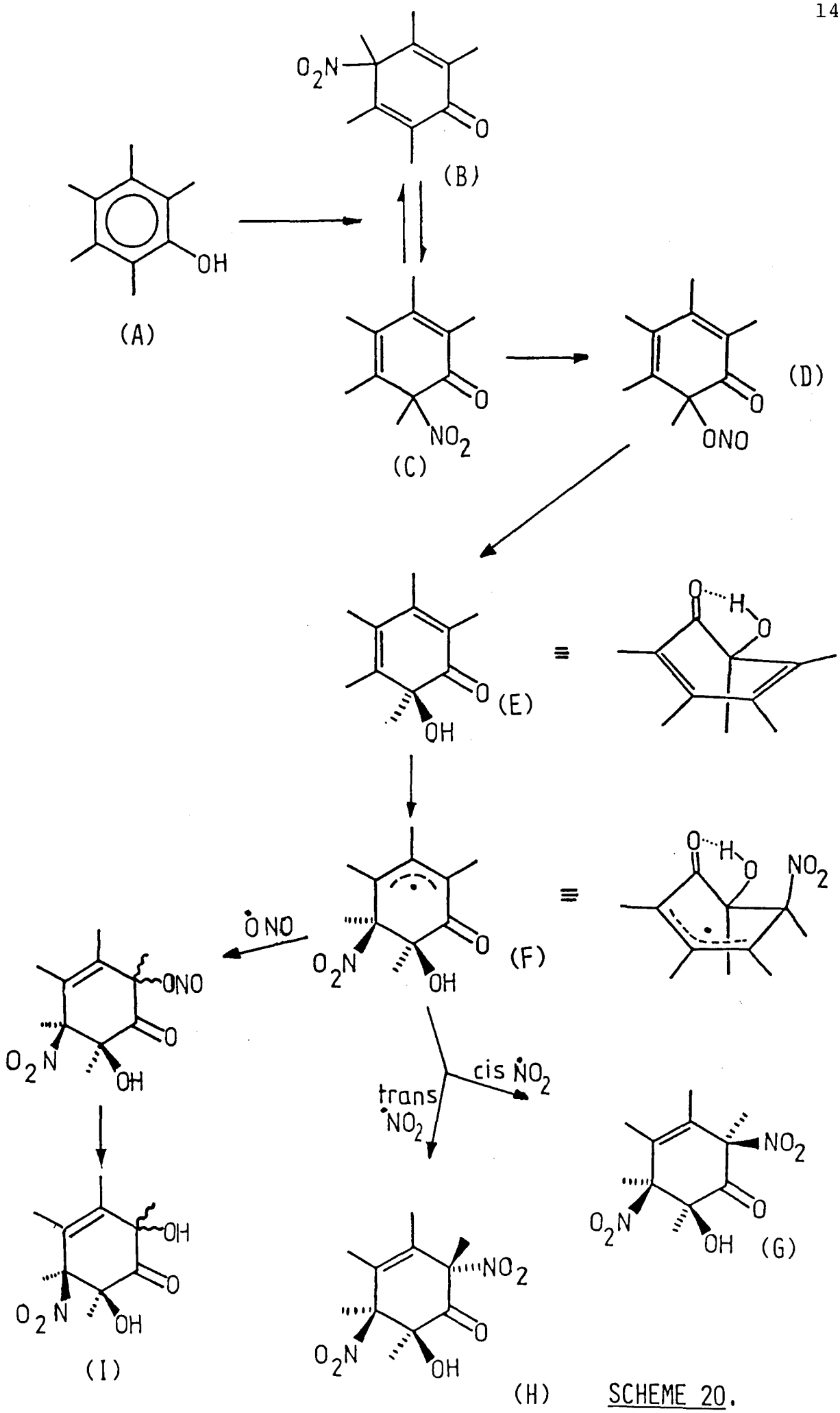
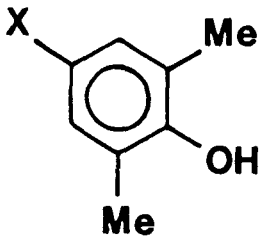

(37)
(38)
(39)
NO_2
NO_2
$\cdot NO_2$
$\dot{N}O_2$
$\dot{O}NO$
$\dot{O}NO$
30% Rearrangement
56% Addition

SCHEME 19.



SCHEME 20.

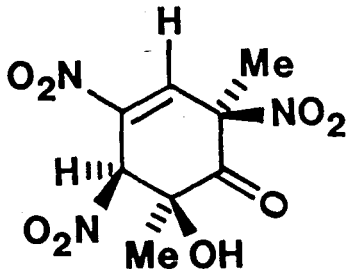
BLOCK D.



(40) (a) X = NO_2

(b) X = Bu^t

(c) X = Br



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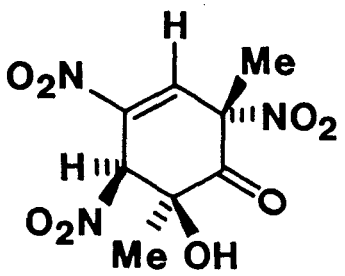
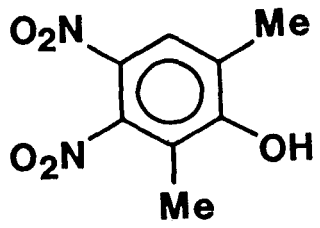


(42)



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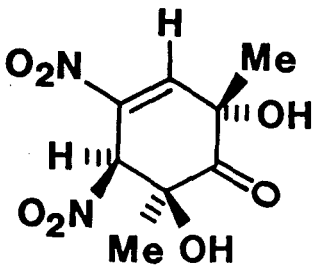

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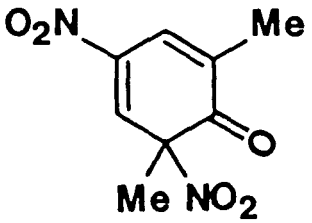

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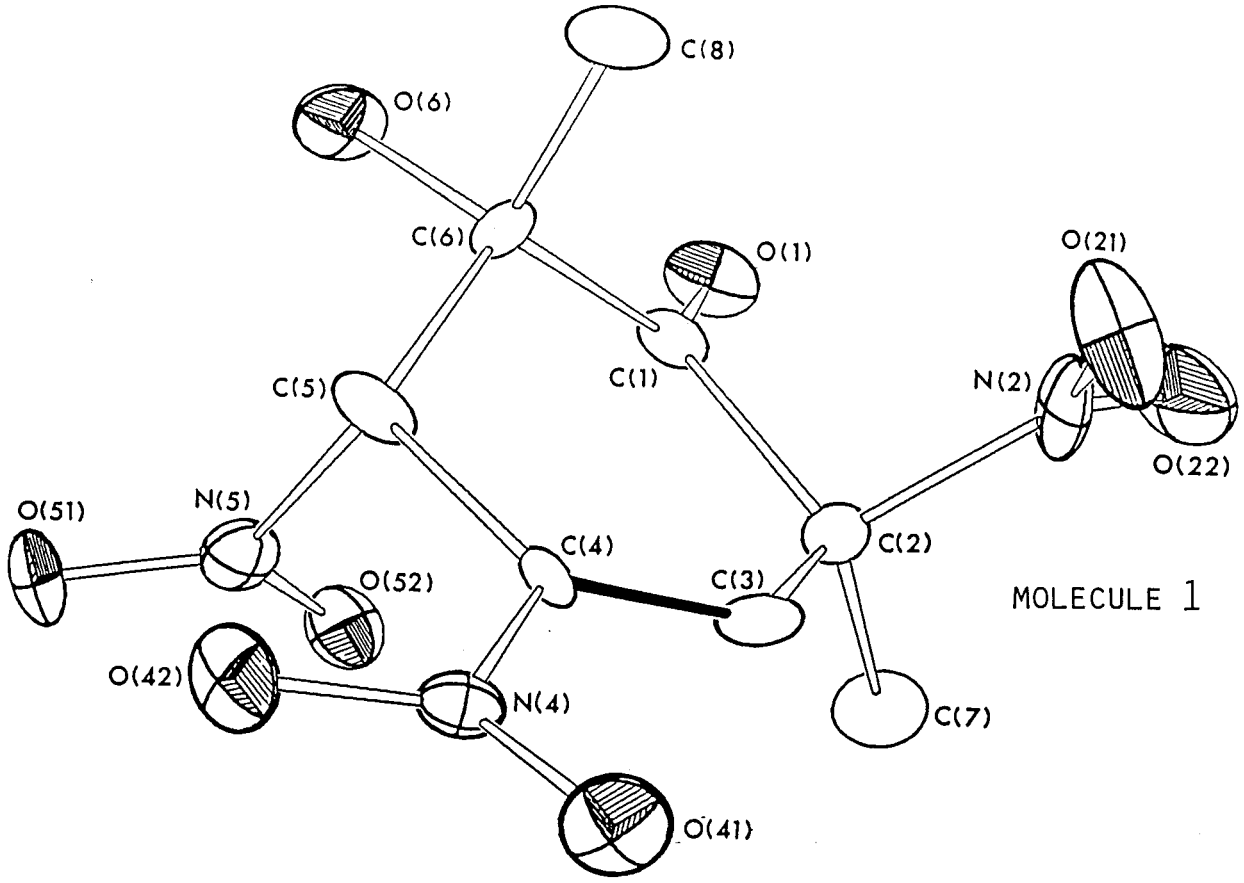

C(8)
O(6)
C(6)
O(1)
O(21)
C(5)
C(1)
N(2)
O(22)
O(51)
N(5)
C(4)
C(2)
O(52)
C(3)
MOLECULE 1
O(42)
N(4)
C(7)
O(41)

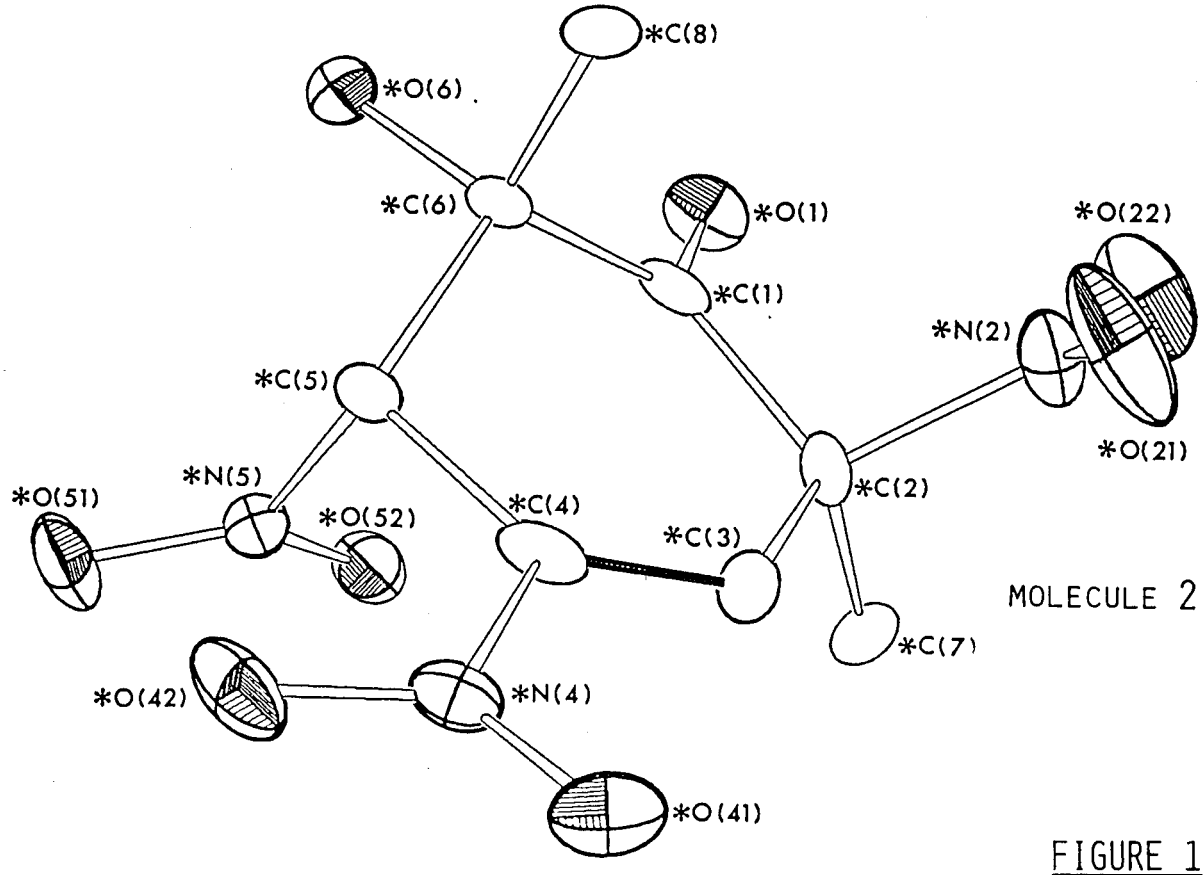
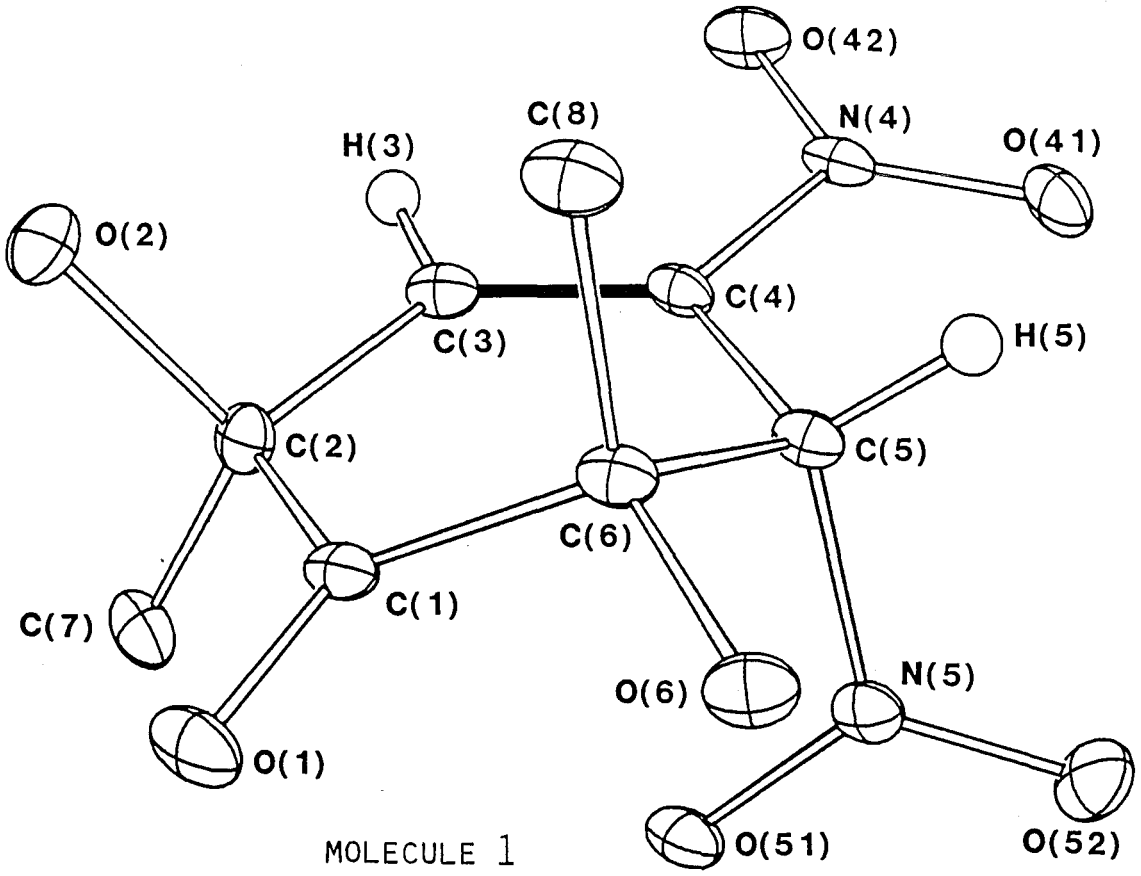
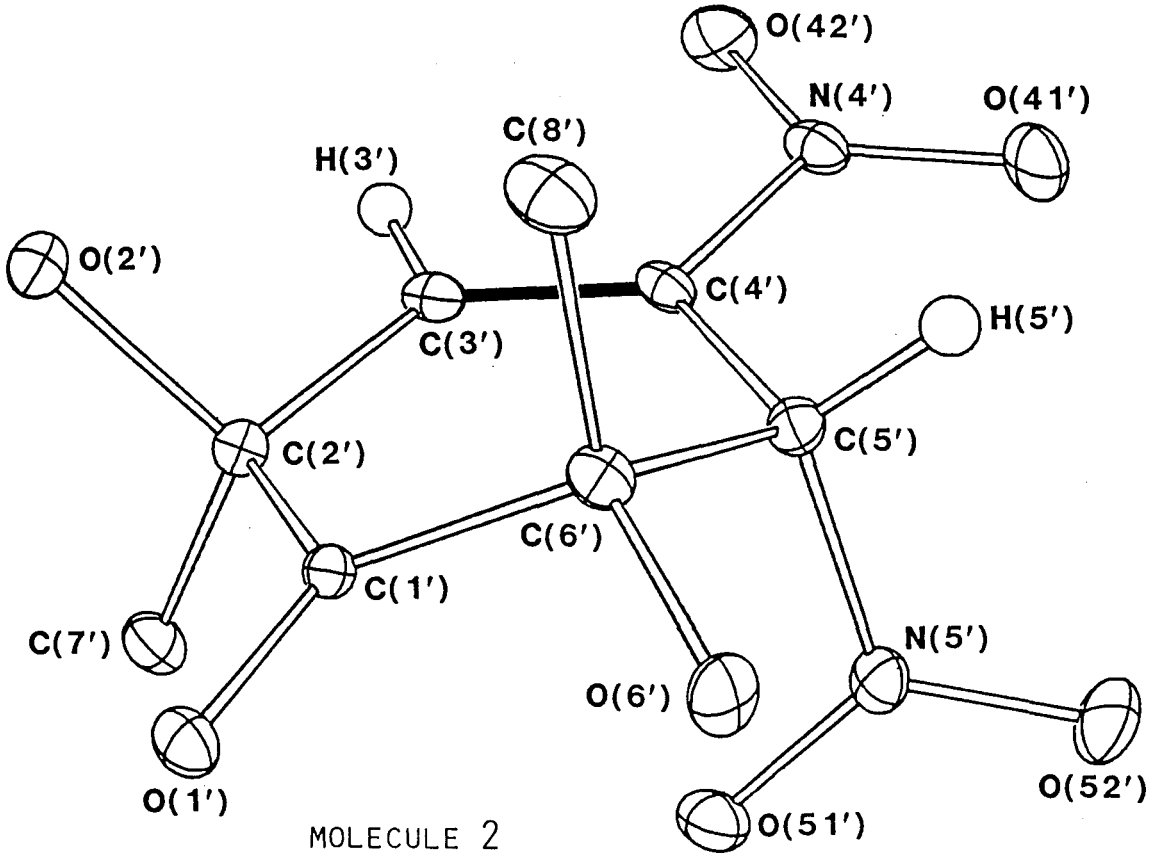

*C(8)
*O(6)
*C(6)
*O(1)
*O(22)
*C(1)
*N(2)
*C(5)
*O(21)
*N(5)
*C(2)
*O(51)
*C(4)
*O(52)
*C(3)
MOLECULE 2
*C(7)
*O(42)
*N(4)
*O(41)

FIGURE 1.



MOLECULE 1

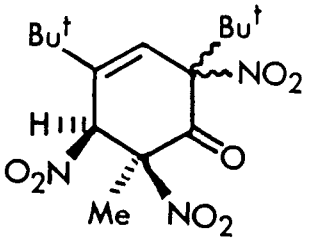


MOLECULE 2

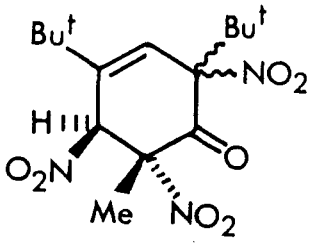
(44)

FIGURE 2.

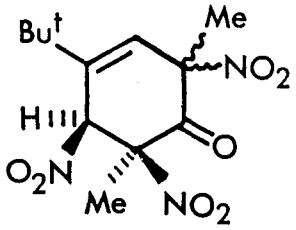
BLOCK E.



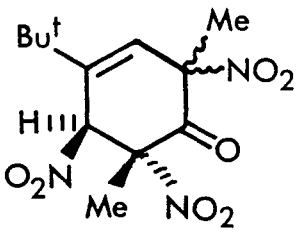
(46)



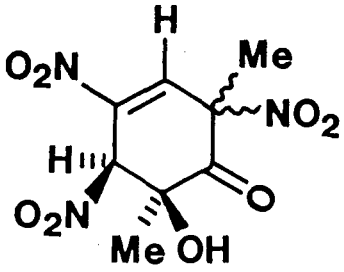
(47)



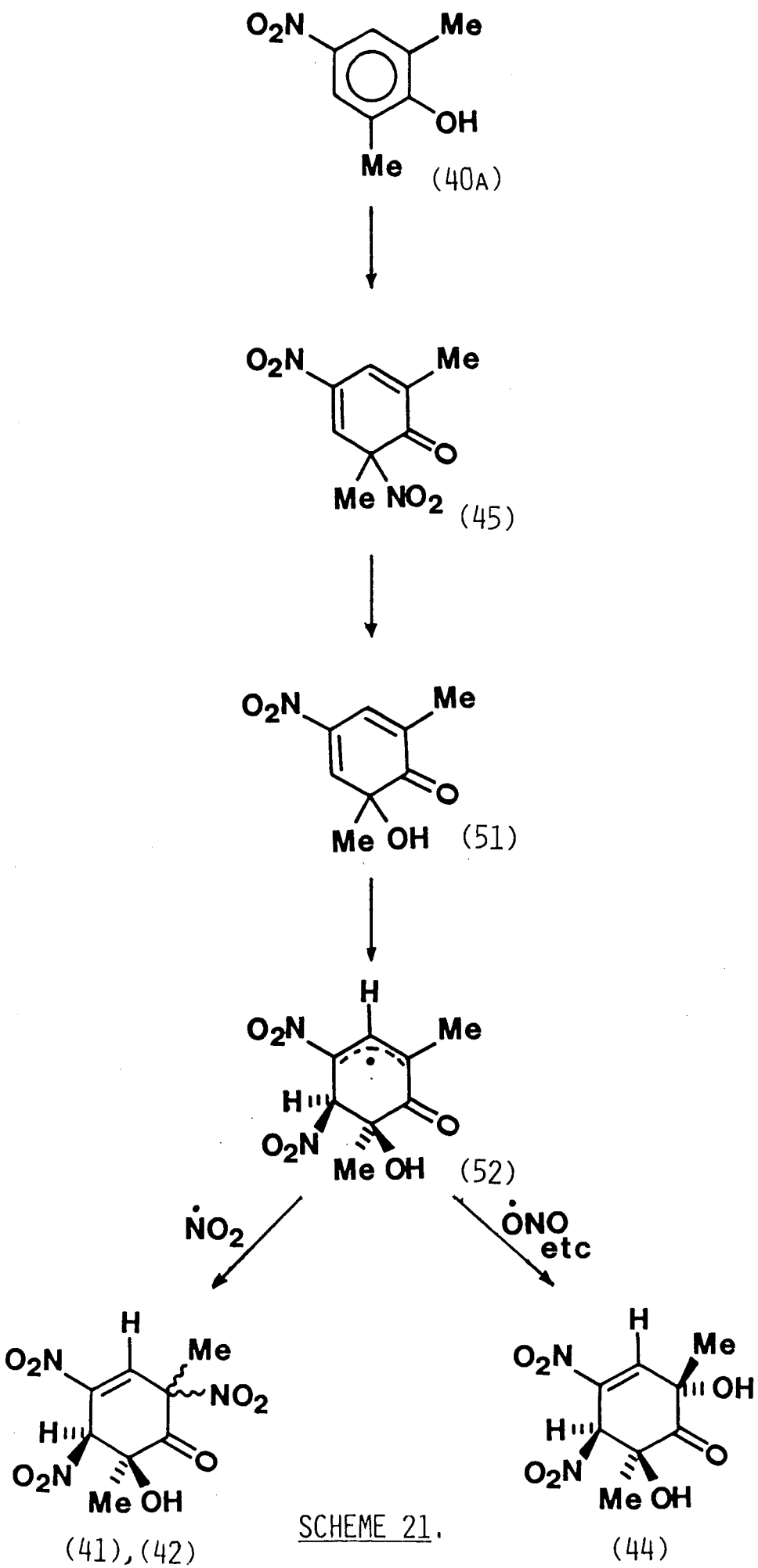
(48)



(49)

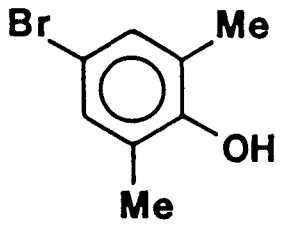


(50)

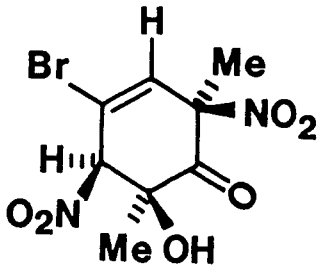

O2N
Me
OH
Me
(40A)
O2N
Me
O
Me NO2
(45)
O2N
Me
O
Me OH
(51)
H
O2N
Me
H
O2N
O
Me OH
(52)
ṄO2
ȮNO
etc
H
O2N
Me
NO2
H
O2N
O
Me OH
(41),(42)
H
O2N
Me
OH
H
O2N
O
Me OH
(44)

SCHEME 21.

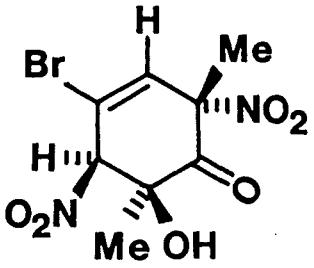
BLOCK F.



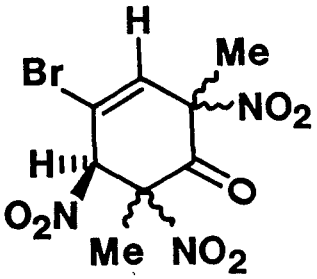
(40c)



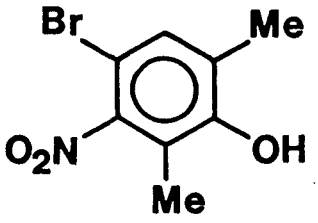
(53)



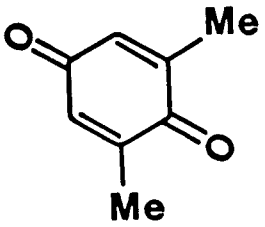
(54)



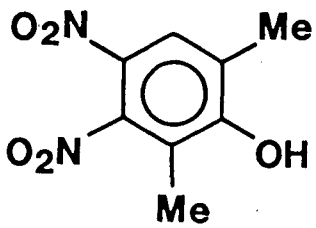
(55)



(58)



(59)



(43)

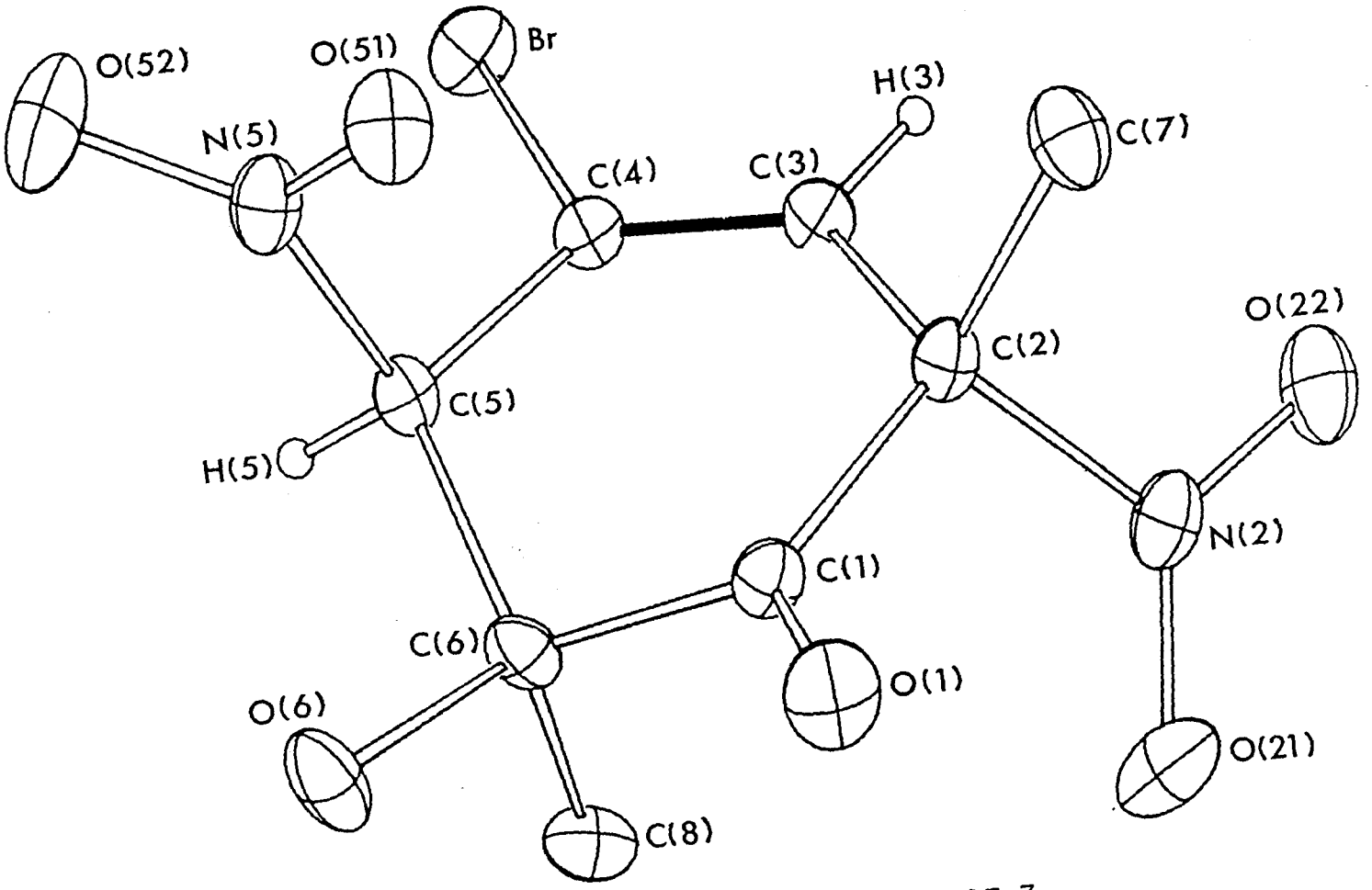
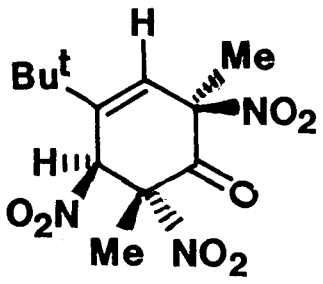


FIGURE 3.

(54)

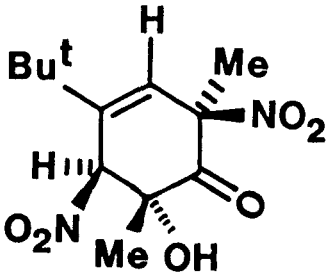
BLOCK G.

δ 6·40



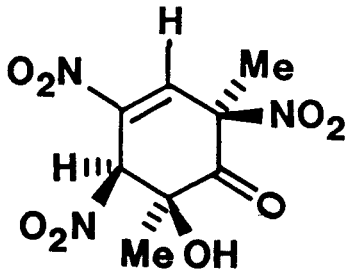
(56)

δ 6·42



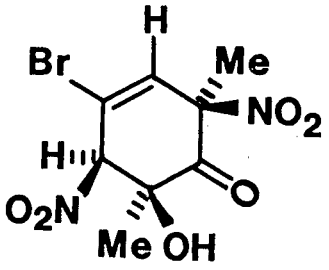
(57)

δ 8·13



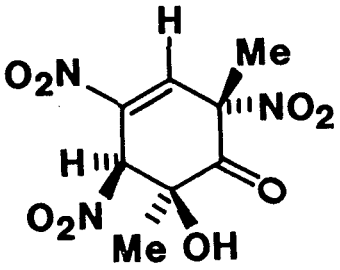
(41)

δ 7·08



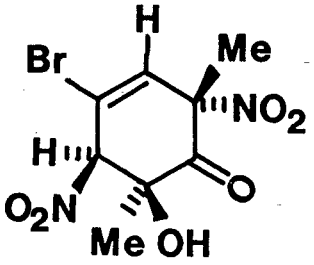
(53)

δ 8·30



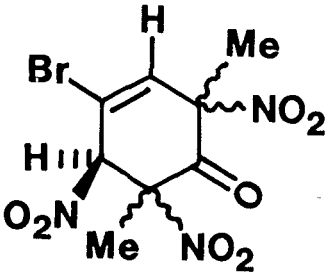
(42)

δ 7·23

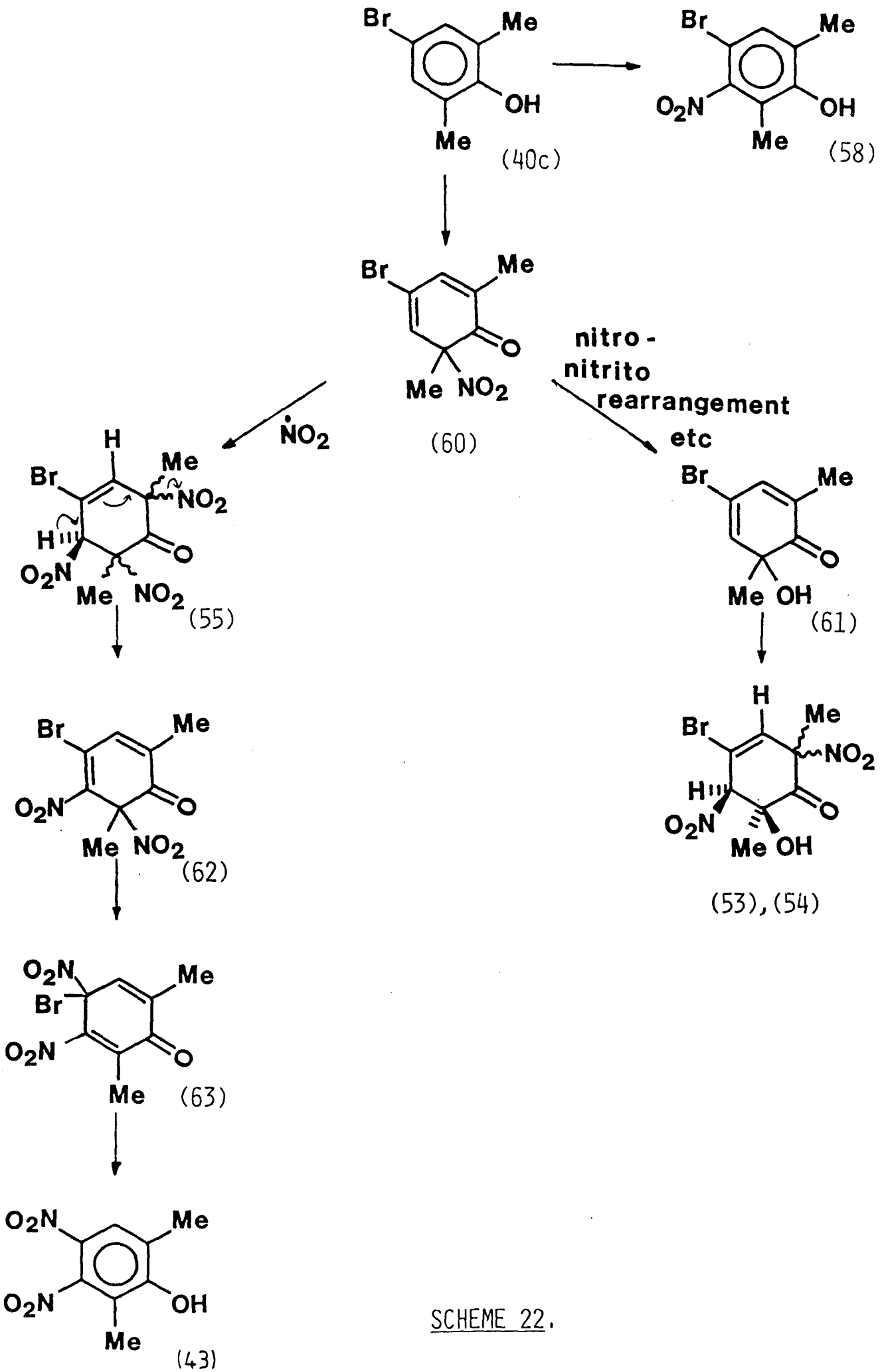


(54)

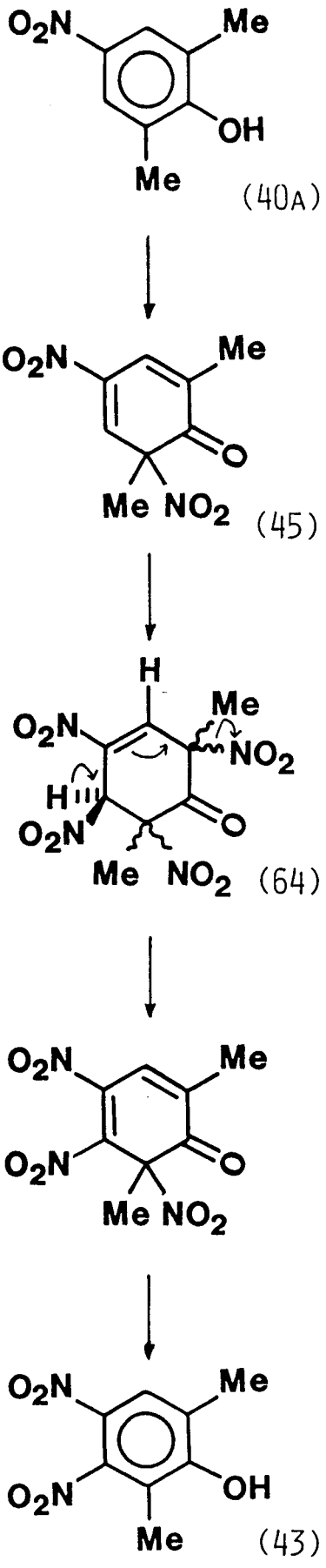
δ 7·25



(55)

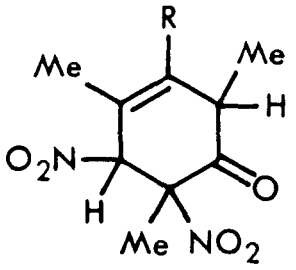

Br
Me
OH
Me
(40c)
Br
Me
O2N
OH
Me
(58)
Br
Me
Me NO2
(60)
nitro -
nitrito
rearrangement
etc
NO2
H
Br
Me
NO2
H
O2N
Me NO2
(55)
Br
Me
Me OH
(61)
Br
Me
O2N
Me NO2
(62)
H
Br
Me
NO2
H
O2N
Me OH
(53), (54)
O2N
Br
Me
O2N
Me
(63)
O2N
Me
O2N
OH
Me
(43)

SCHEME 22.

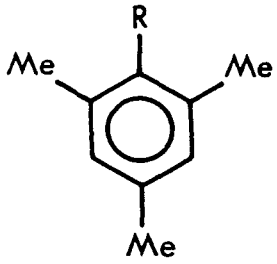

O2N
Me
OH
Me
(40A)
O2N
Me
O
Me NO2
(45)
H
Me
O2N
NO2
H
O2N
O
Me NO2
(64)
O2N
Me
O2N
O
Me NO2
O2N
Me
O2N
OH
Me
(43)

SCHEME 23.

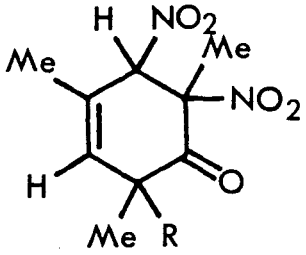
BLOCK H.



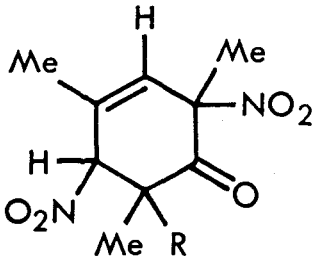
(65) (a) R = Me
(b) R = Et



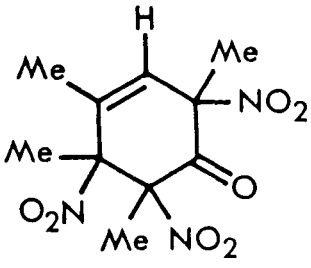
(66) (a) R = Me
(b) R = Et



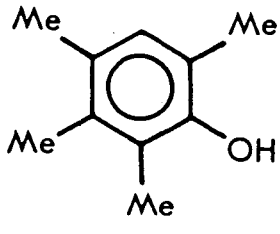
(67) (a) R = Me
(b) R = Et



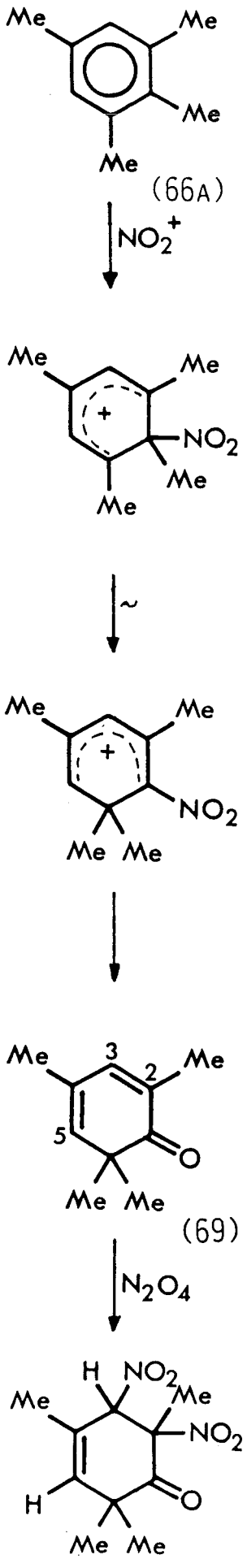
(68) (a) R = Me
(b) R = Et



(70)

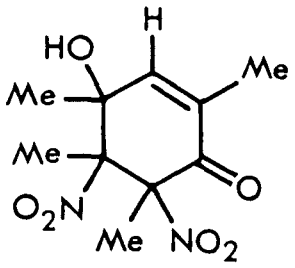


(71)

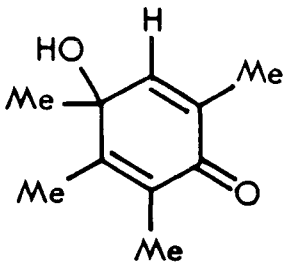

Me
Me
Me
Me
(66A)
NO_2^+
Me
Me
+
NO_2
Me
Me
~
Me
Me
+
NO_2
Me Me
3
2
Me
Me
5
O
Me Me
(69)
N_2O_4
H
NO_2
Me
Me
NO_2
H
O
Me Me
(67A)

SCHEME 24.

BLOCK I.

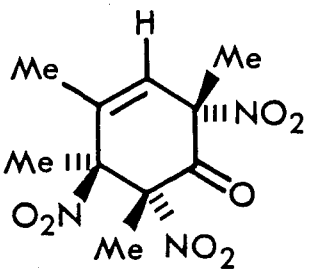


(72)



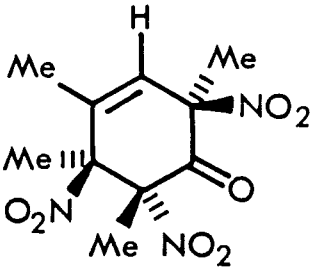
(73)

δ 6·47



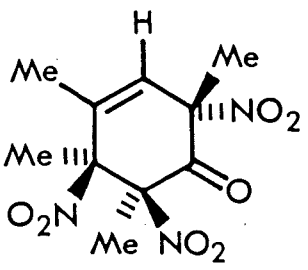
(74)

δ 6·30



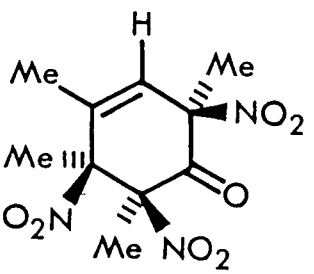
(75)

δ 6·33



(76)

δ 6·23



(77)

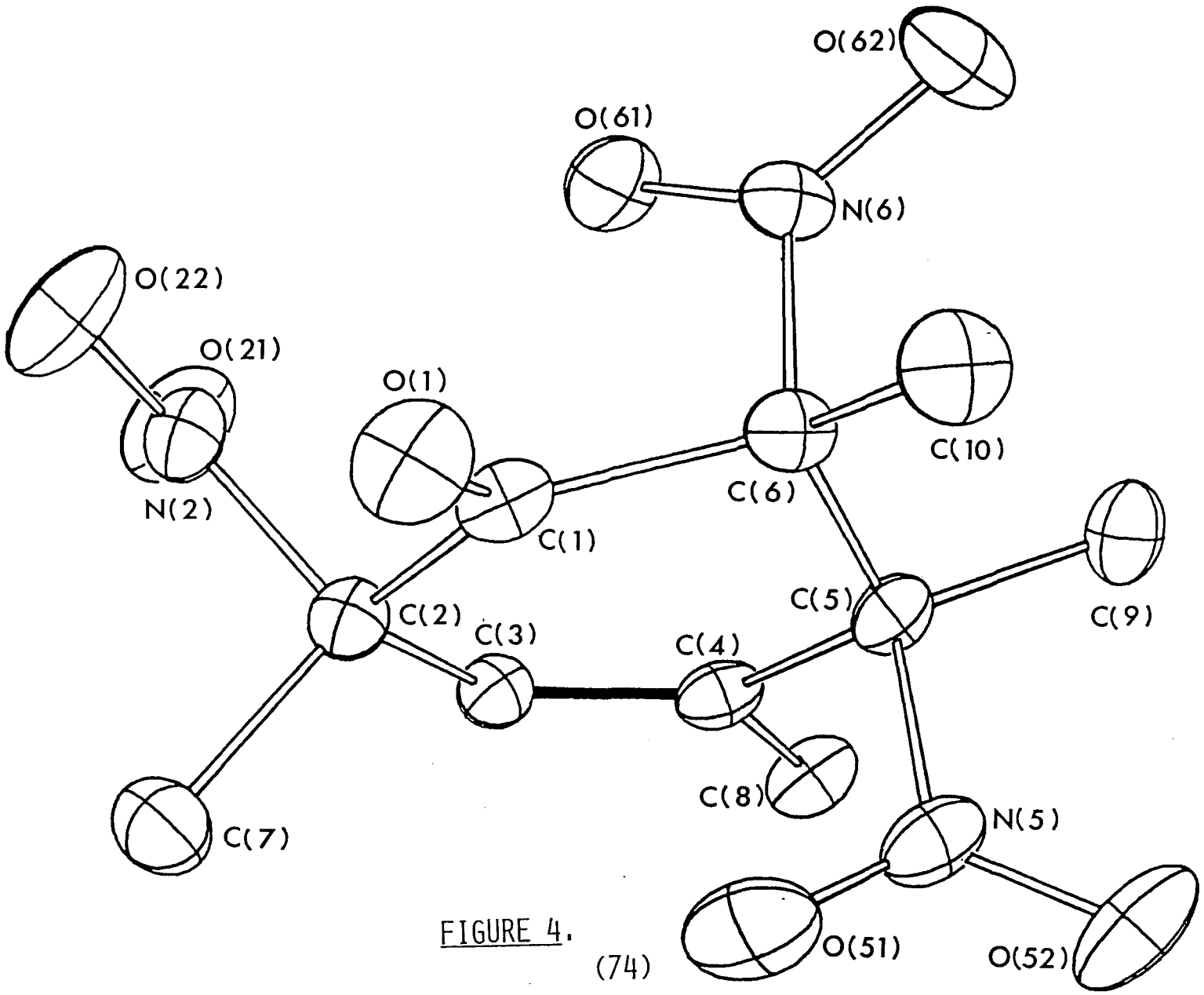
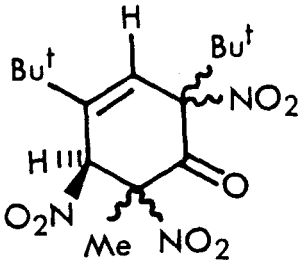


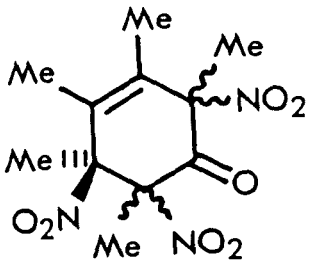
FIGURE 4.

(74)

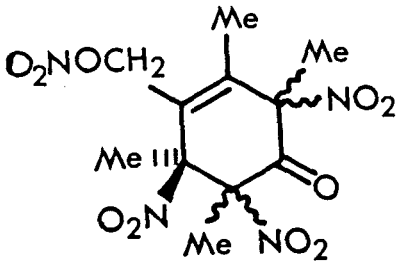
BLOCK J.



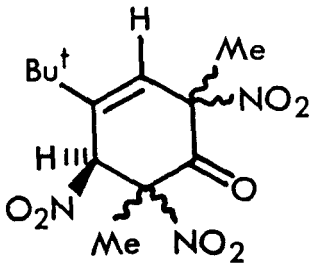
(78)



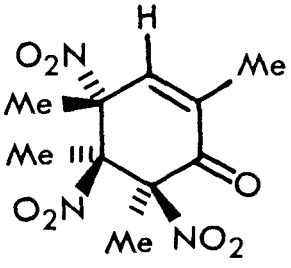
(79)



(80)



(81)



(82)

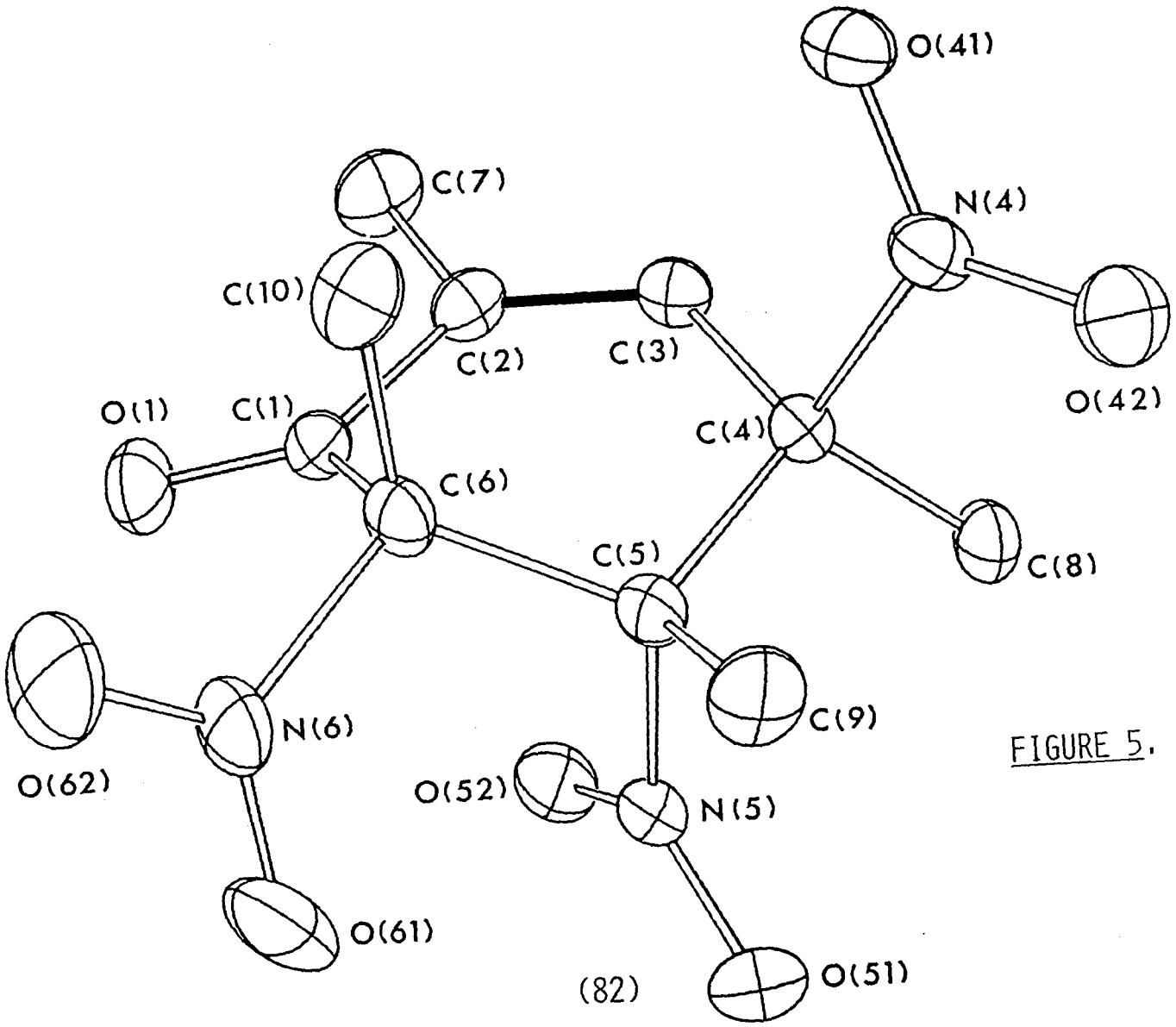
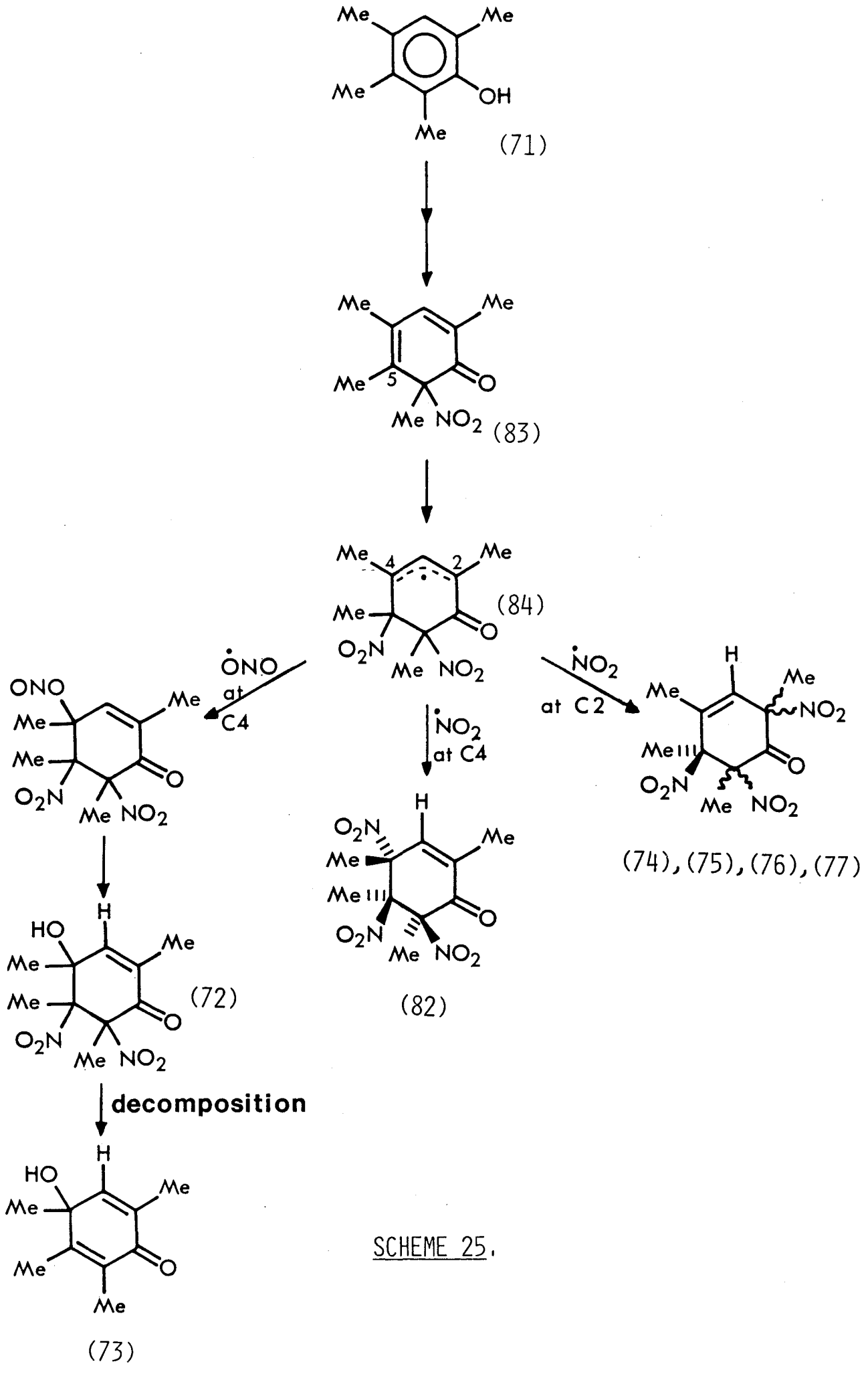
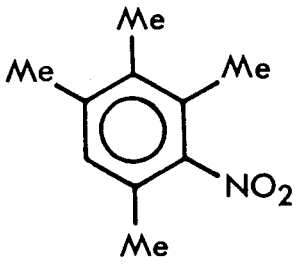


FIGURE 5.

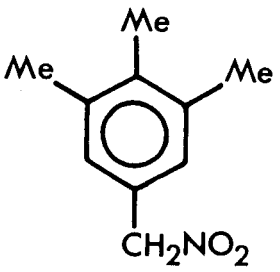

Me
Me
Me
OH
Me
(71)
Me
Me
Me
5
O
Me NO2
(83)
Me
4
2
Me
Me
O2N
O
Me NO2
(84)
ONO
at
C4
NO2
at C4
NO2
at C2
ONO
Me
Me
Me
O2N
O
Me NO2
H
HO
Me
Me
Me
O2N
O
Me NO2
(72)
decomposition
H
HO
Me
Me
Me
O
Me
(73)
H
O2N
Me
Me
Me III
O2N
O
Me NO2
(82)
H
Me
Me
NO2
Me III
O2N
O
Me NO2
(74), (75), (76), (77)

SCHEME 25.

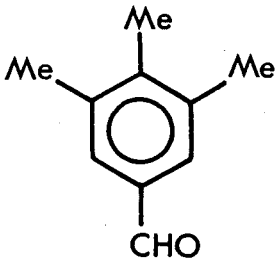
BLOCK K.



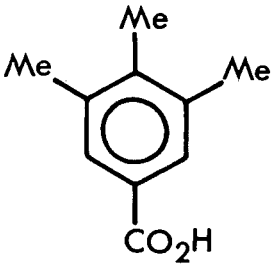
(85)



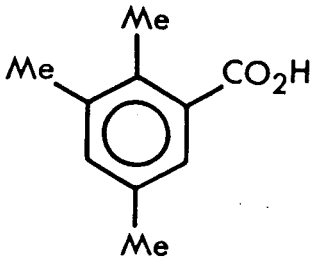
(86)



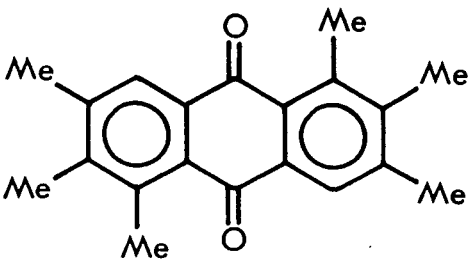
(87)



(88)

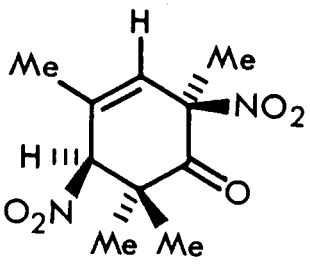


(89)

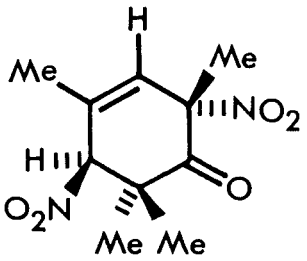


(90)

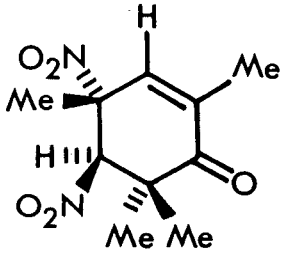
BLOCK L.



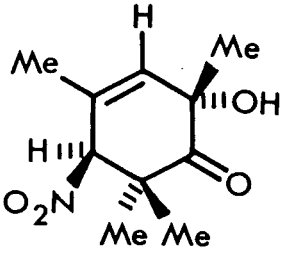
(91)



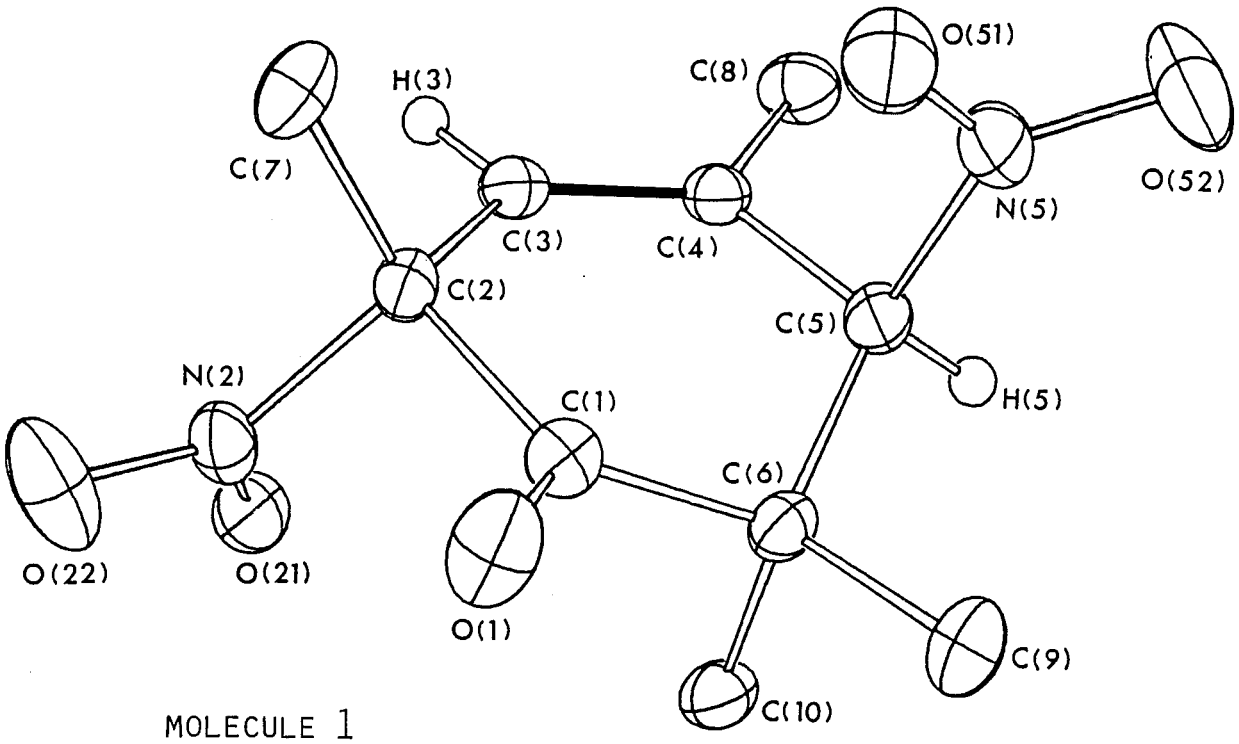
(92)



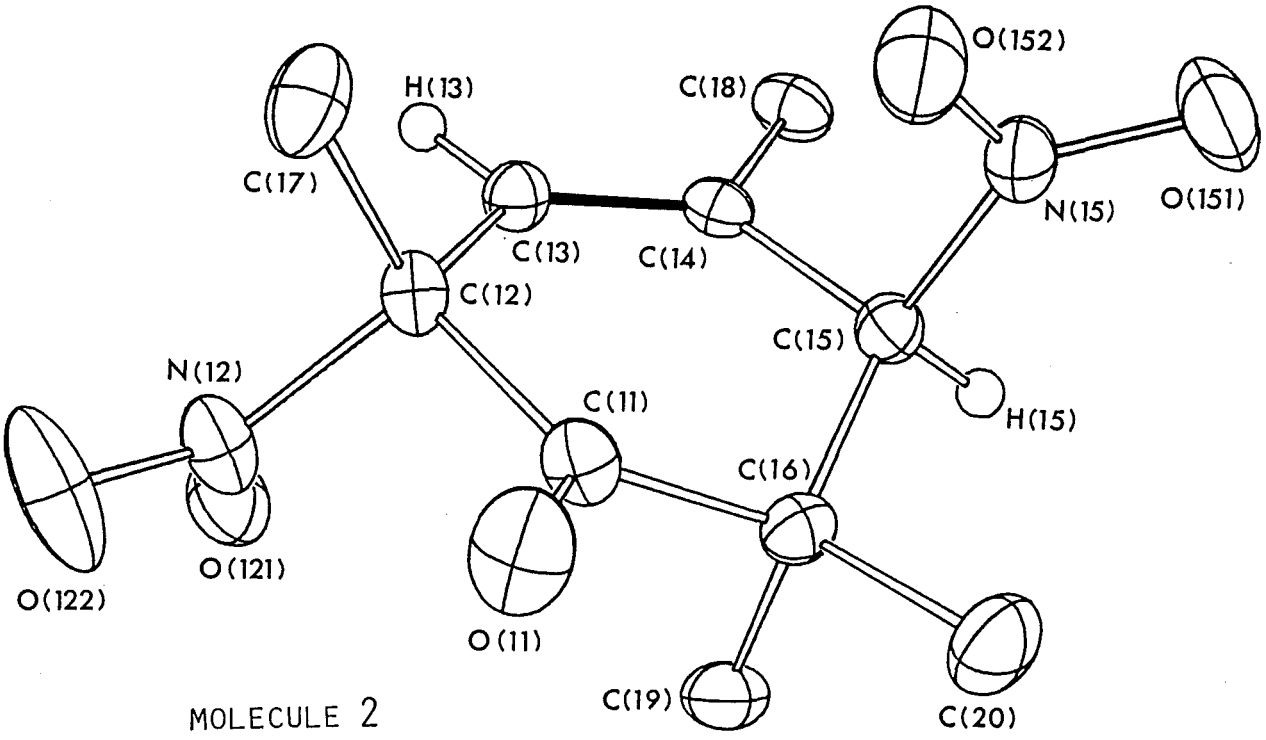
(93)



(94)



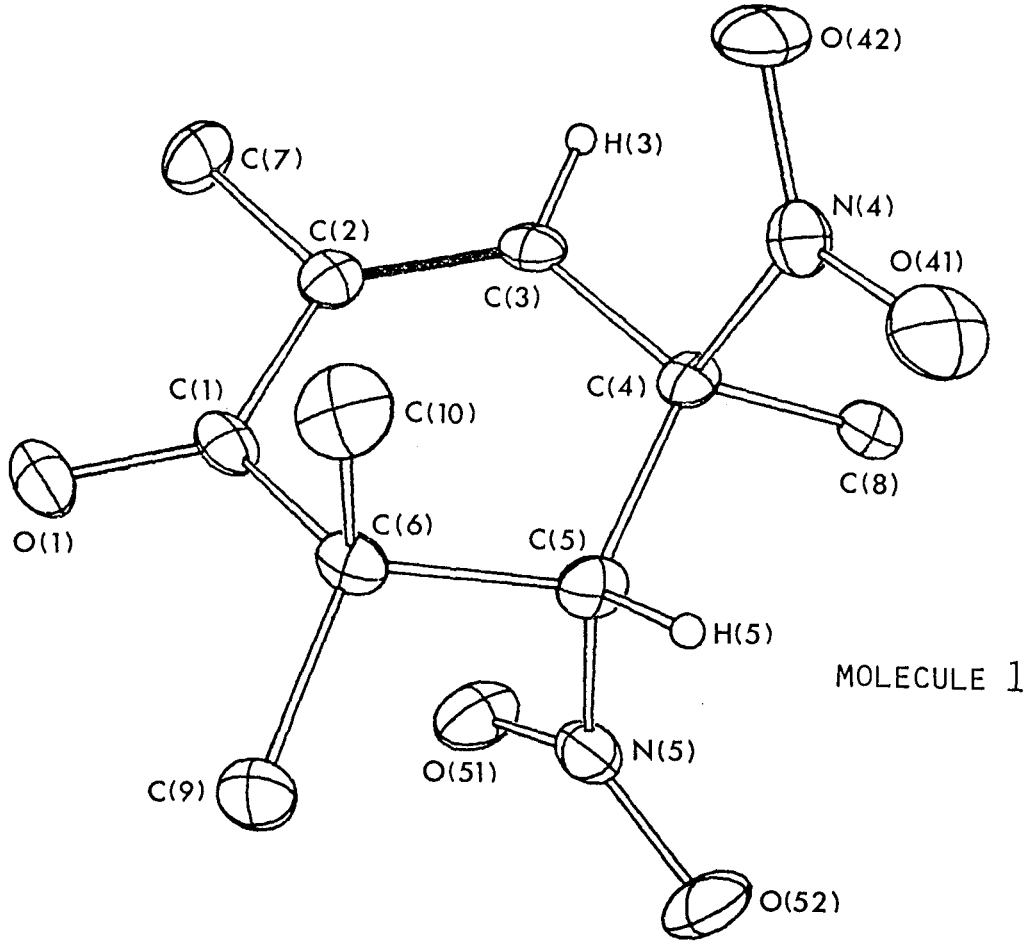
MOLECULE 1



MOLECULE 2

(92)

FIGURE 6.


O(42)
C(7)
H(3)
N(4)
C(2)
O(41)
C(3)
C(1)
C(4)
C(10)
C(8)
O(1)
C(6)
C(5)
H(5)
MOLECULE 1
O(51)
N(5)
C(9)
O(52)

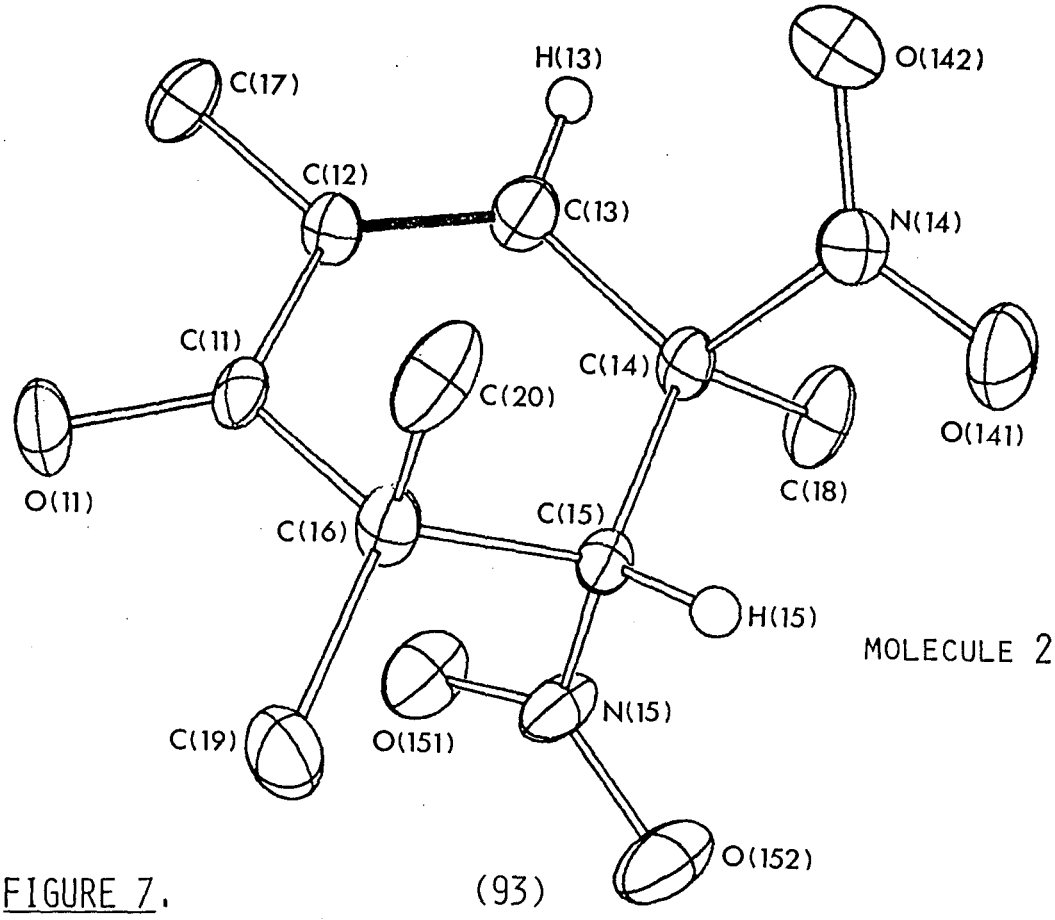

H(13)
O(142)
C(17)
C(12)
C(13)
N(14)
C(11)
C(14)
C(20)
O(141)
O(11)
C(18)
C(16)
C(15)
H(15)
MOLECULE 2
C(19)
O(151)
N(15)
O(152)

FIGURE 7. (93)

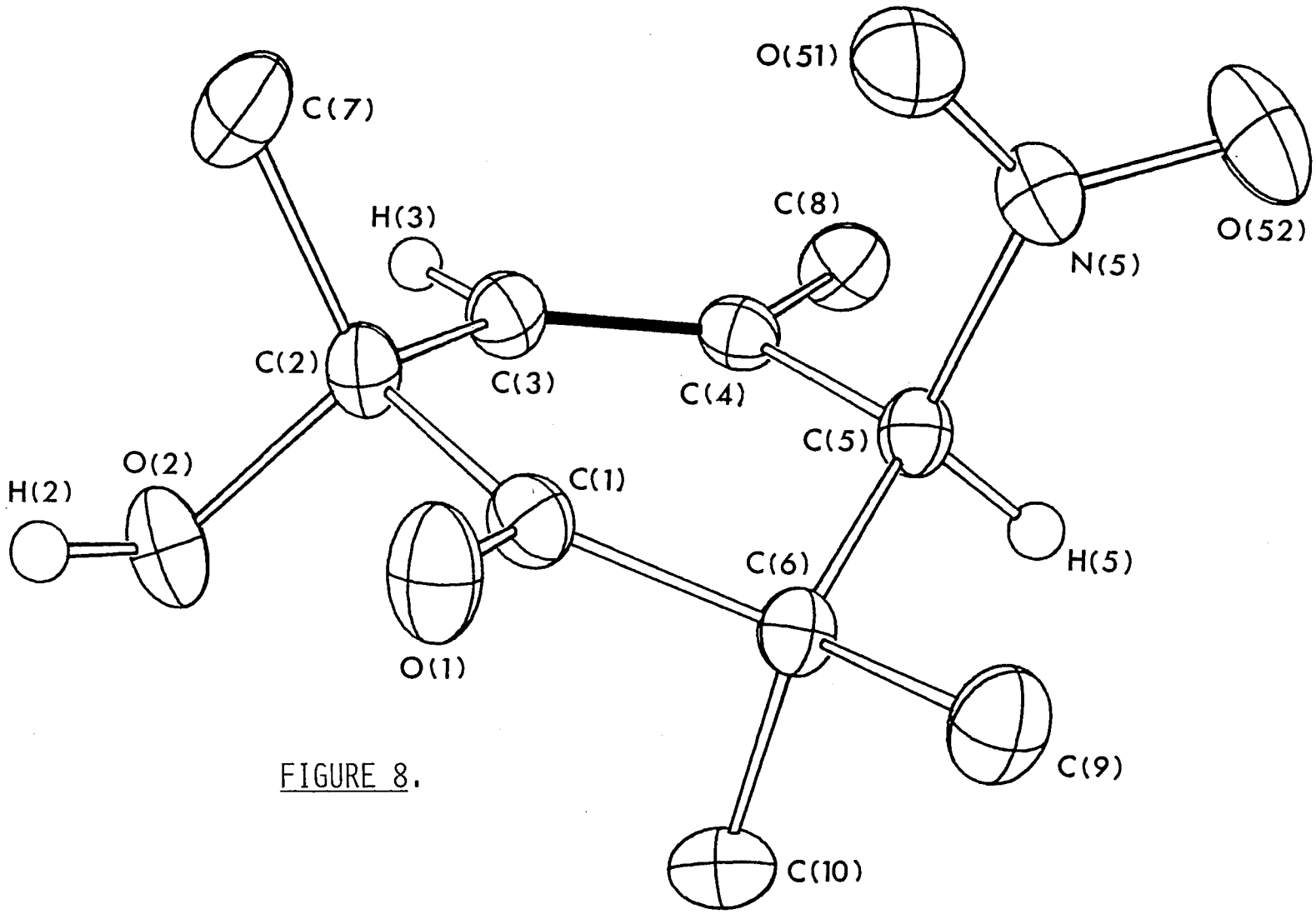
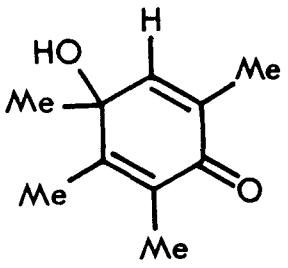


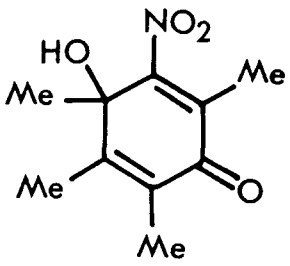
FIGURE 8.

(94)

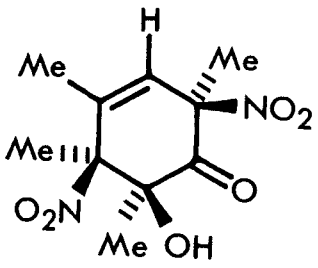
BLOCK M.



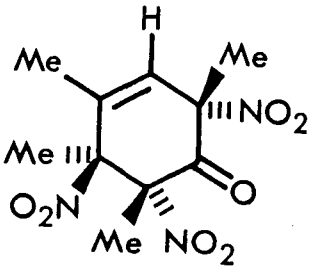
(73)



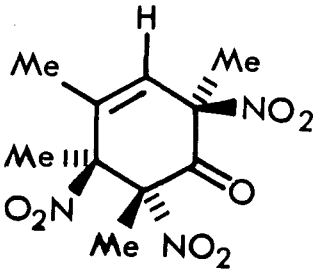
(95)



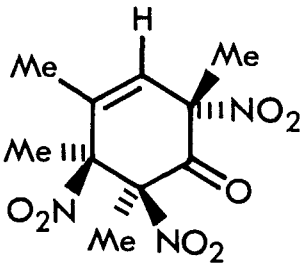
(96)



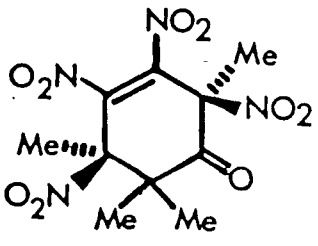
(74)



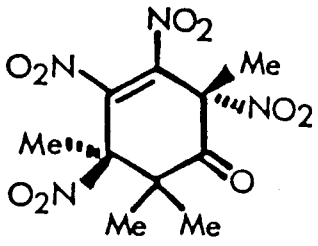
(75)



(76)



(18)



(19)

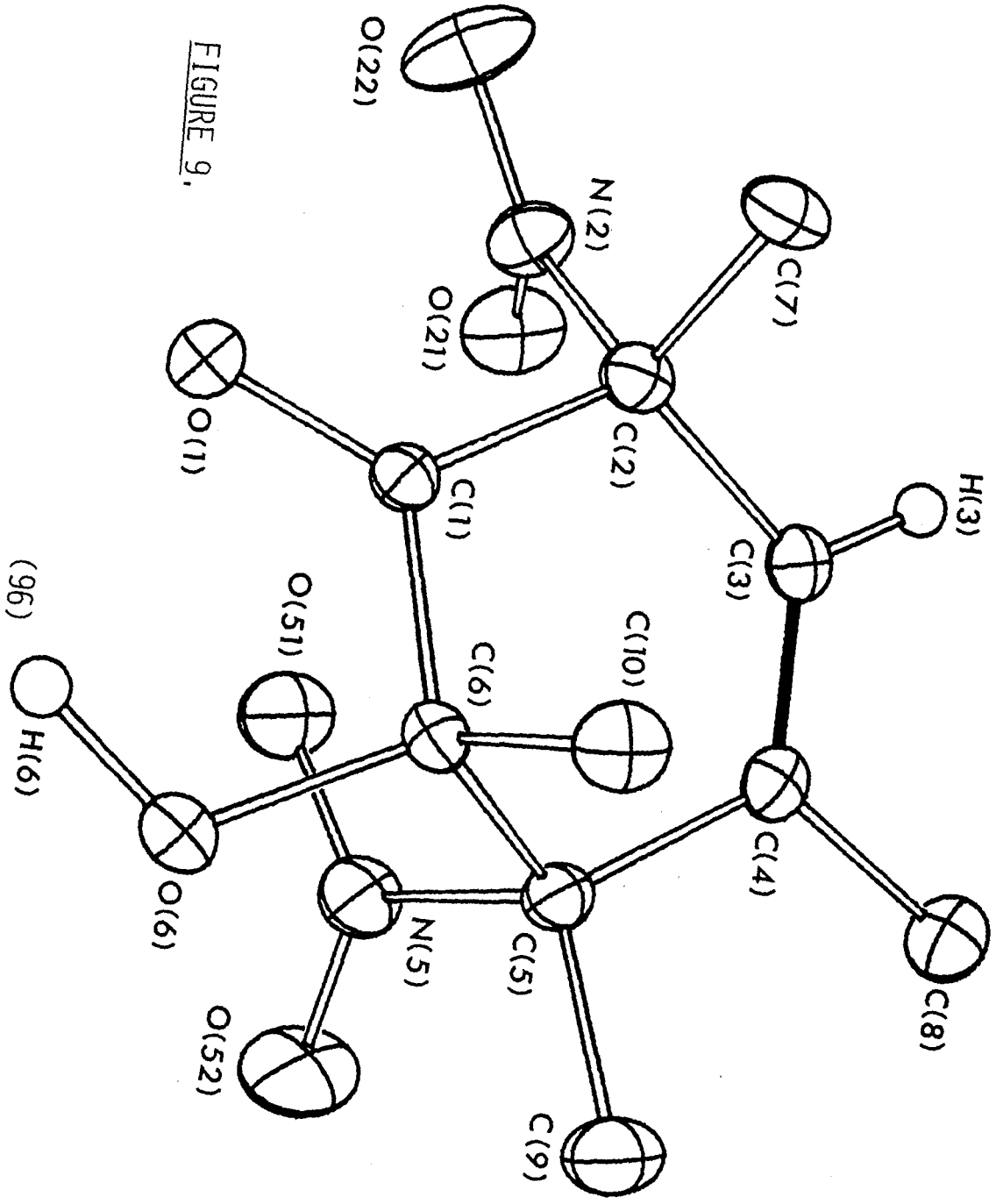
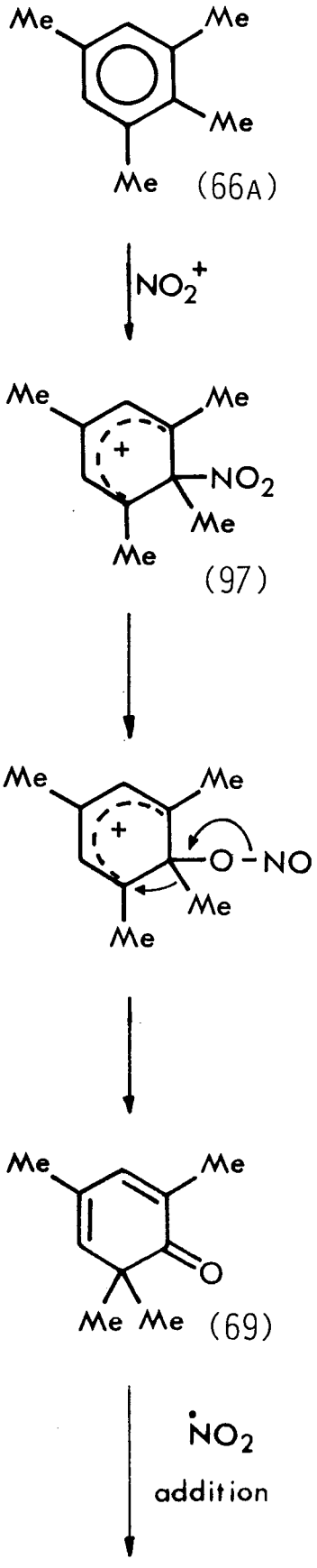
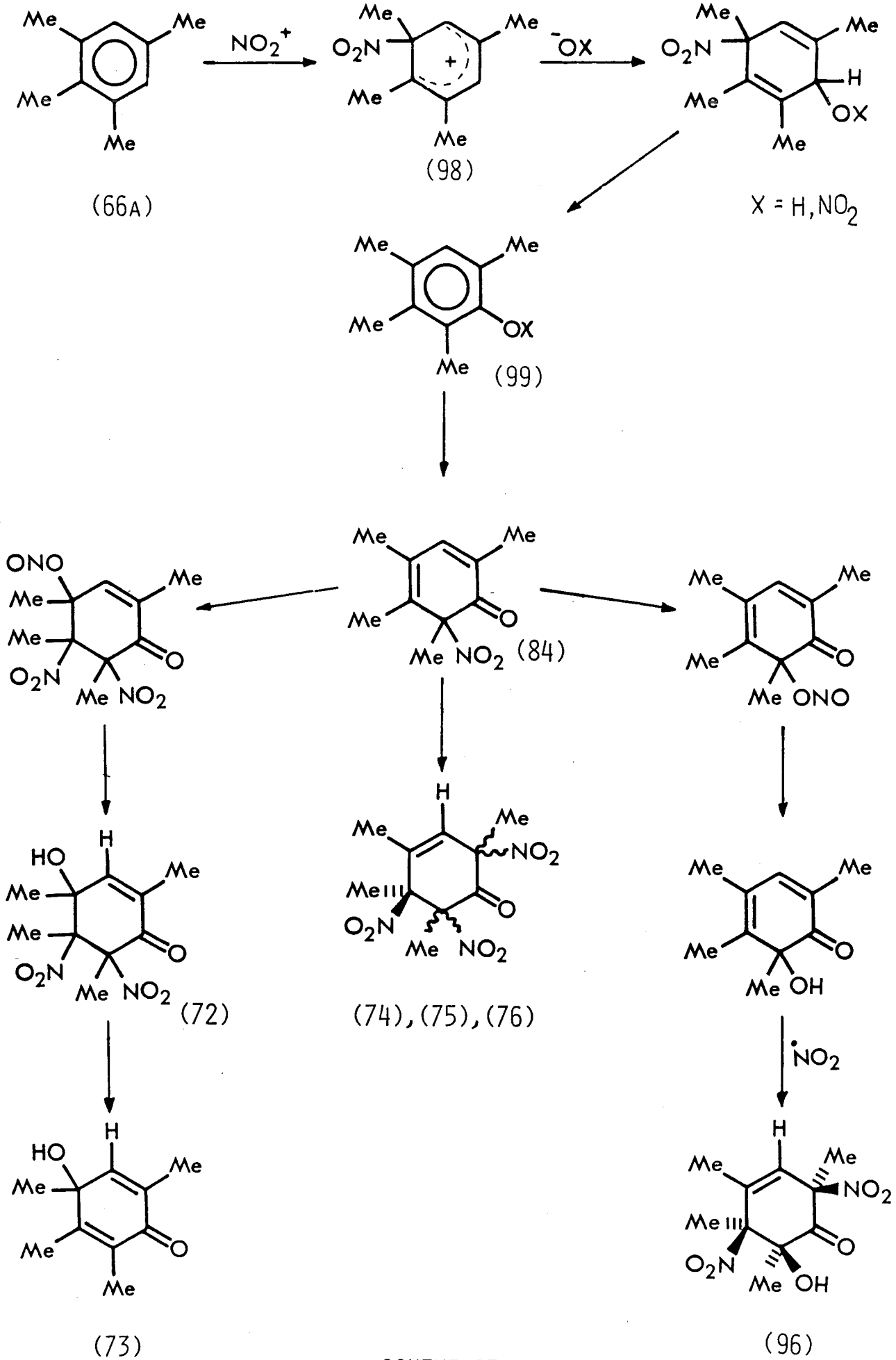


FIGURE 9.



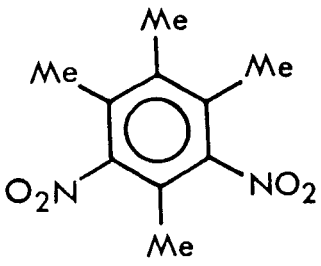
(91),(92),(93),(94)

SCHEME 26.

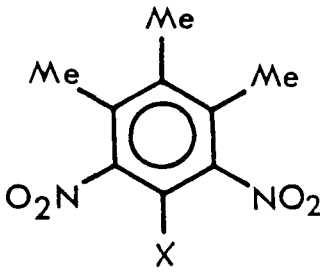


SCHEME 27.

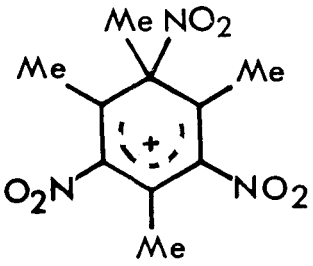
BLOCK N.



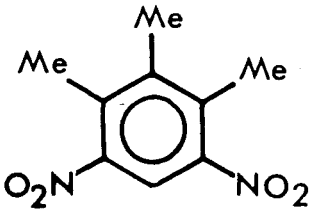
(100)



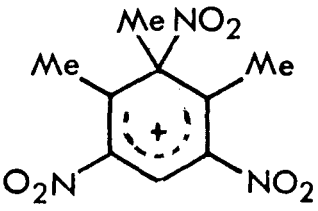
(101) (a) X = CHO
(b) X = CH_2NO_2
(c) X = CH_2OH
(d) X = CO_2H



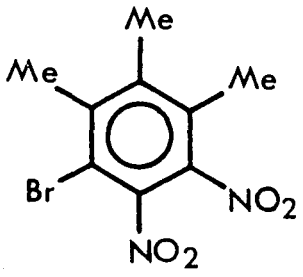
(102)



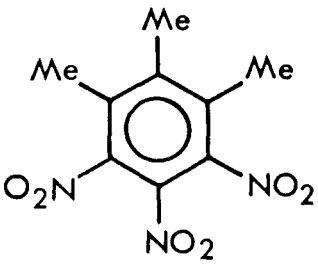
(103)



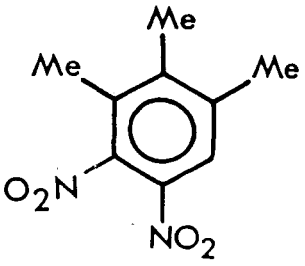
(104)



(105)

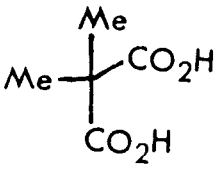


(106)

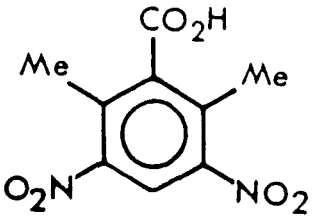


(107)

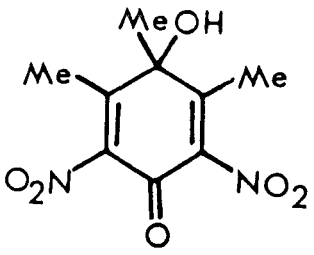
BLOCK O.



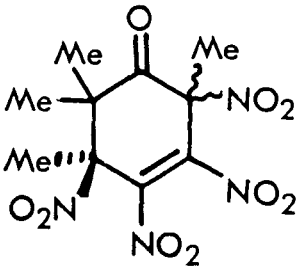
(108)



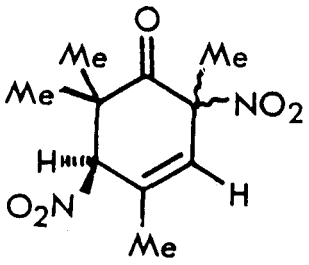
(109)



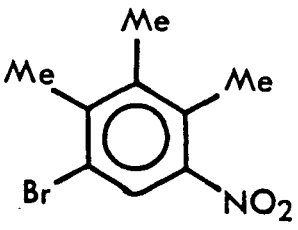
(110)



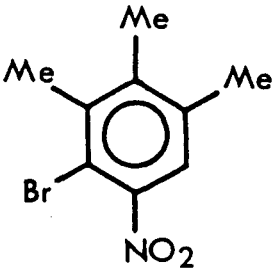
(15)



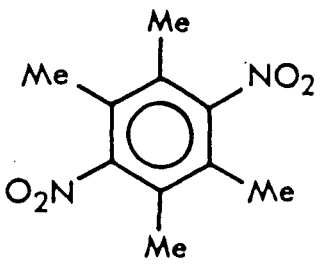
(68A)



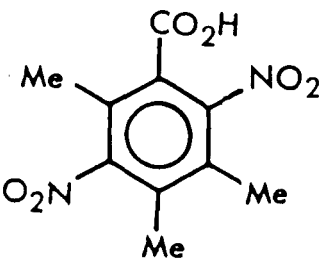
(115)



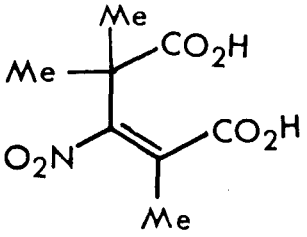
(116)



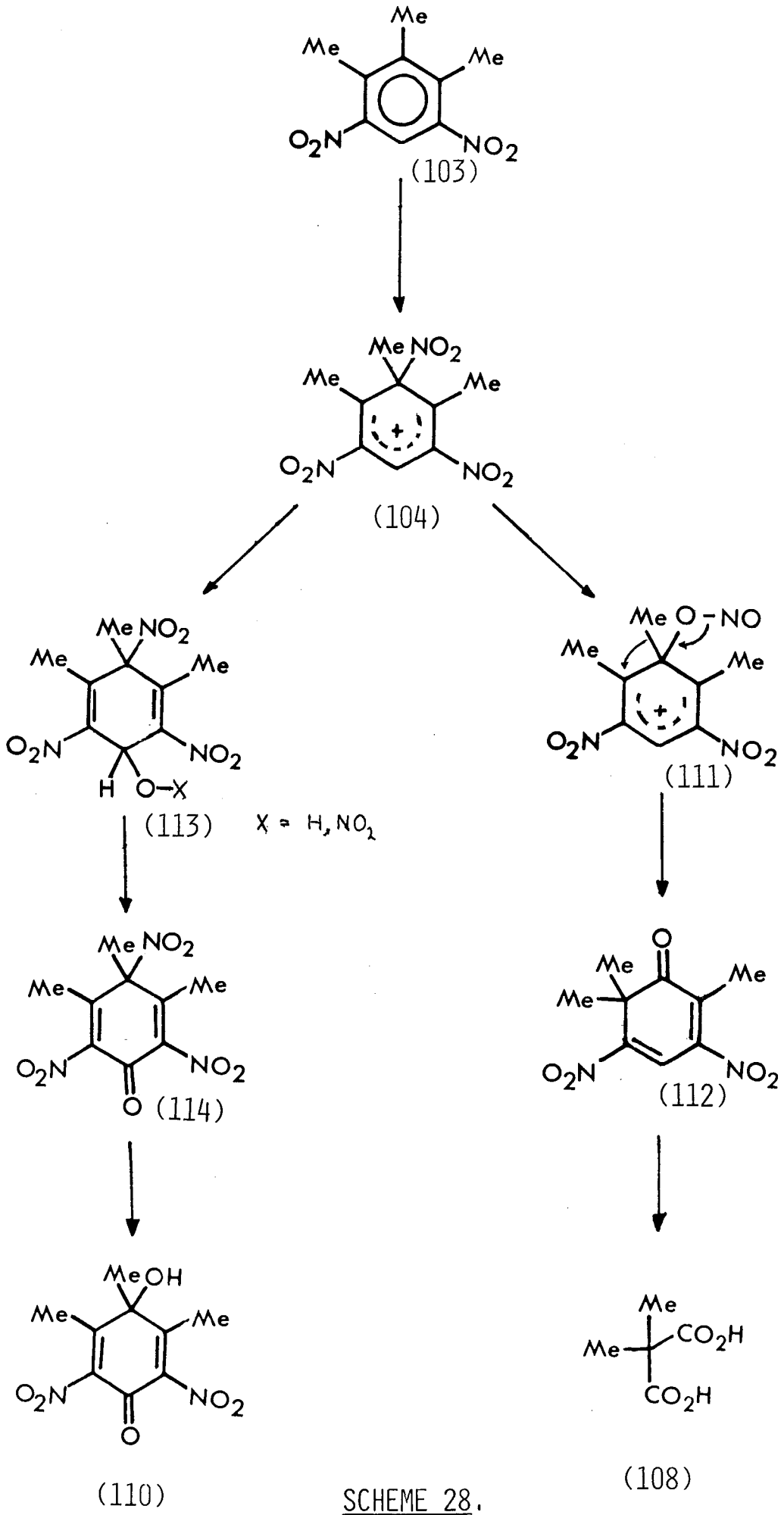
(117)



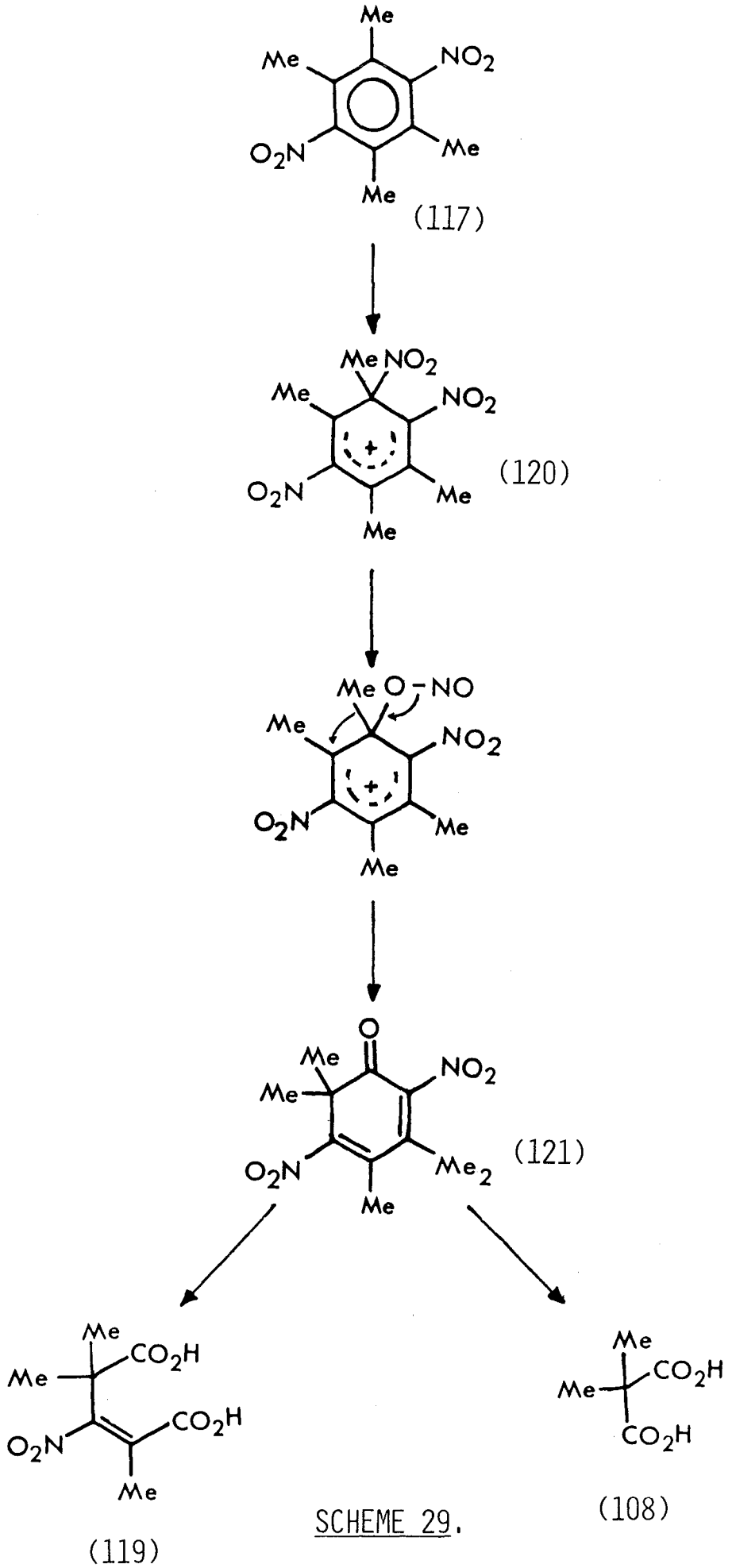
(118)



(119)

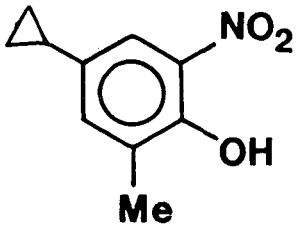

Me
Me
Me
O_2N
NO_2
(103)
Me NO_2
Me
Me
O_2N
NO_2
(104)
Me NO_2
Me
Me
O_2N
NO_2
H O–X
(113)
X = H, NO_2
Me O–NO
Me
Me
O_2N
NO_2
(111)
Me NO_2
Me
Me
O_2N
NO_2
O (114)
O
Me
Me
Me
O_2N
NO_2
(112)
Me OH
Me
Me
O_2N
NO_2
O
(110)
Me
Me
CO_2H
CO_2H
(108)

SCHEME 28.

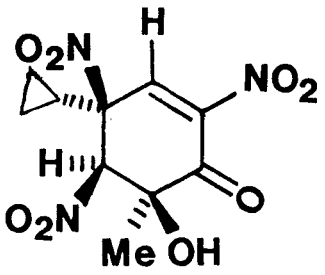

Me
Me
NO2
O2N
Me
Me
(117)
Me NO2
Me
NO2
O2N
Me
Me
(120)
Me O-NO
Me
NO2
O2N
Me
Me
O
Me
Me
NO2
O2N
Me2
Me
(121)
Me
CO2H
Me
CO2H
O2N
Me
(119)
Me
CO2H
Me
CO2H
(108)

SCHEME 29.

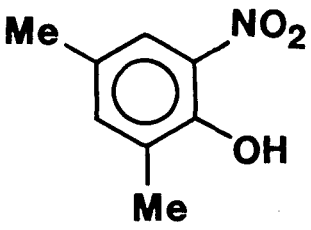
BLOCK P.



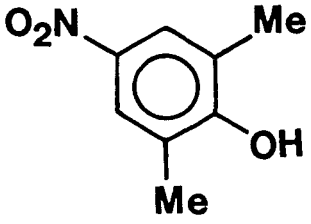
(122)



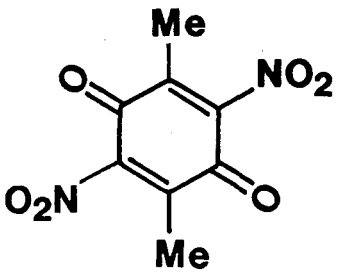
(123)



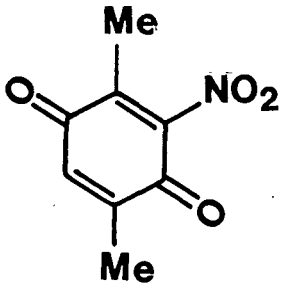
(128)



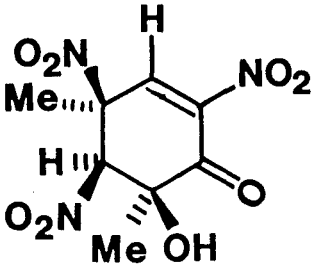
(40A)



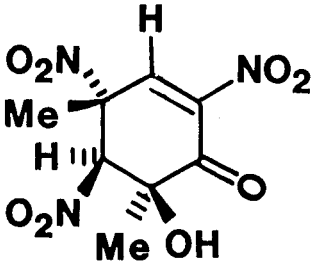
(129)



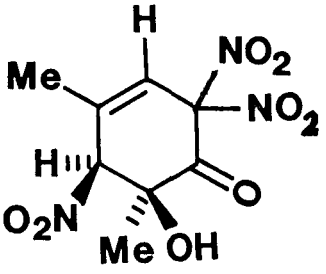
(130)



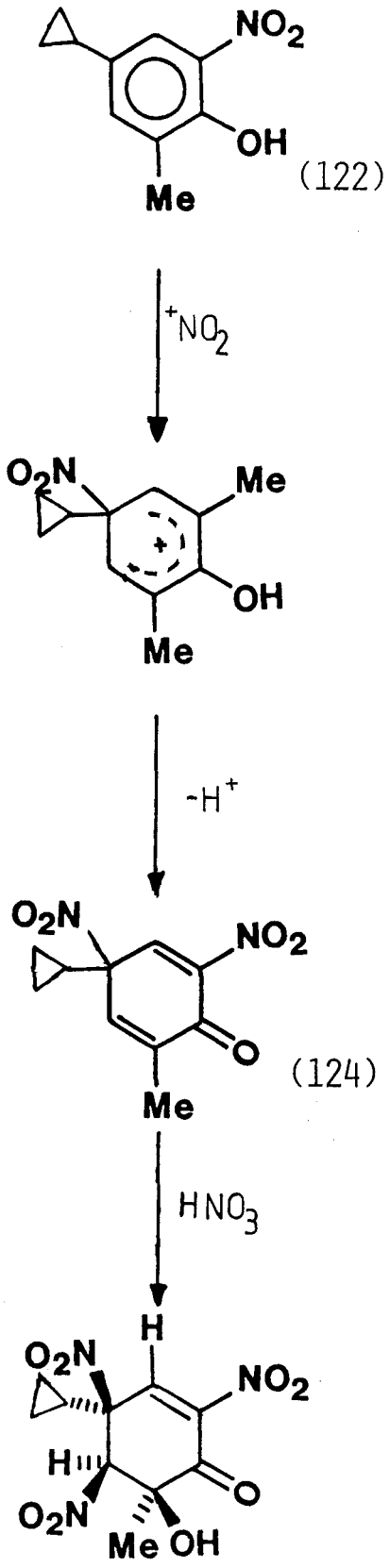
(131)



(132)

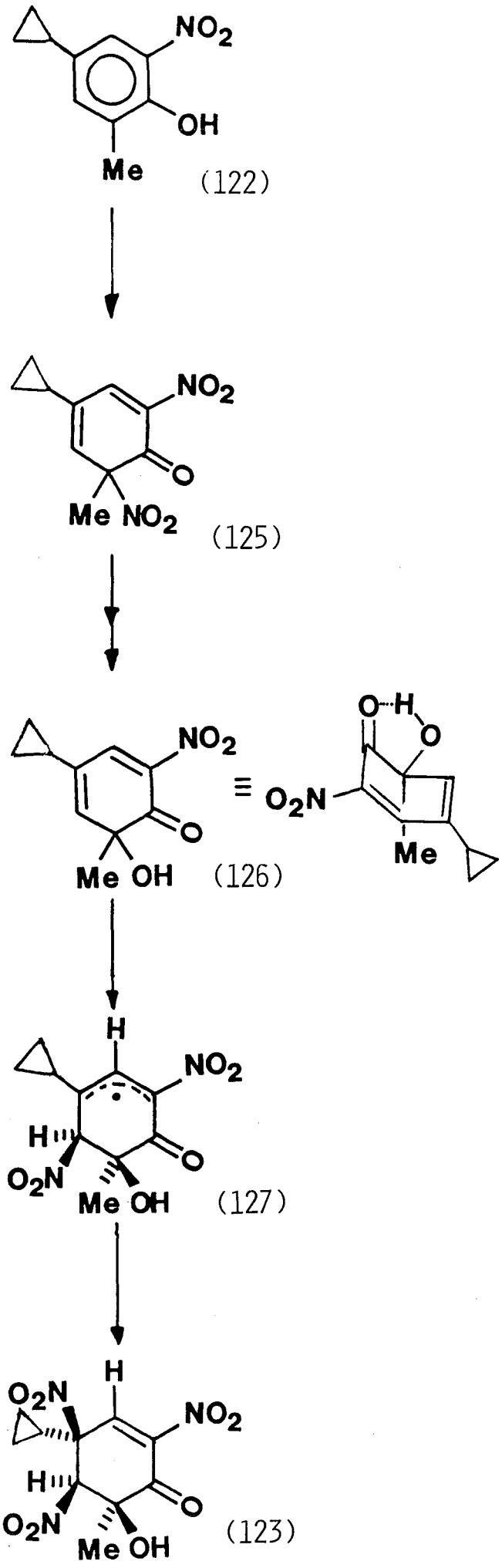


(133)

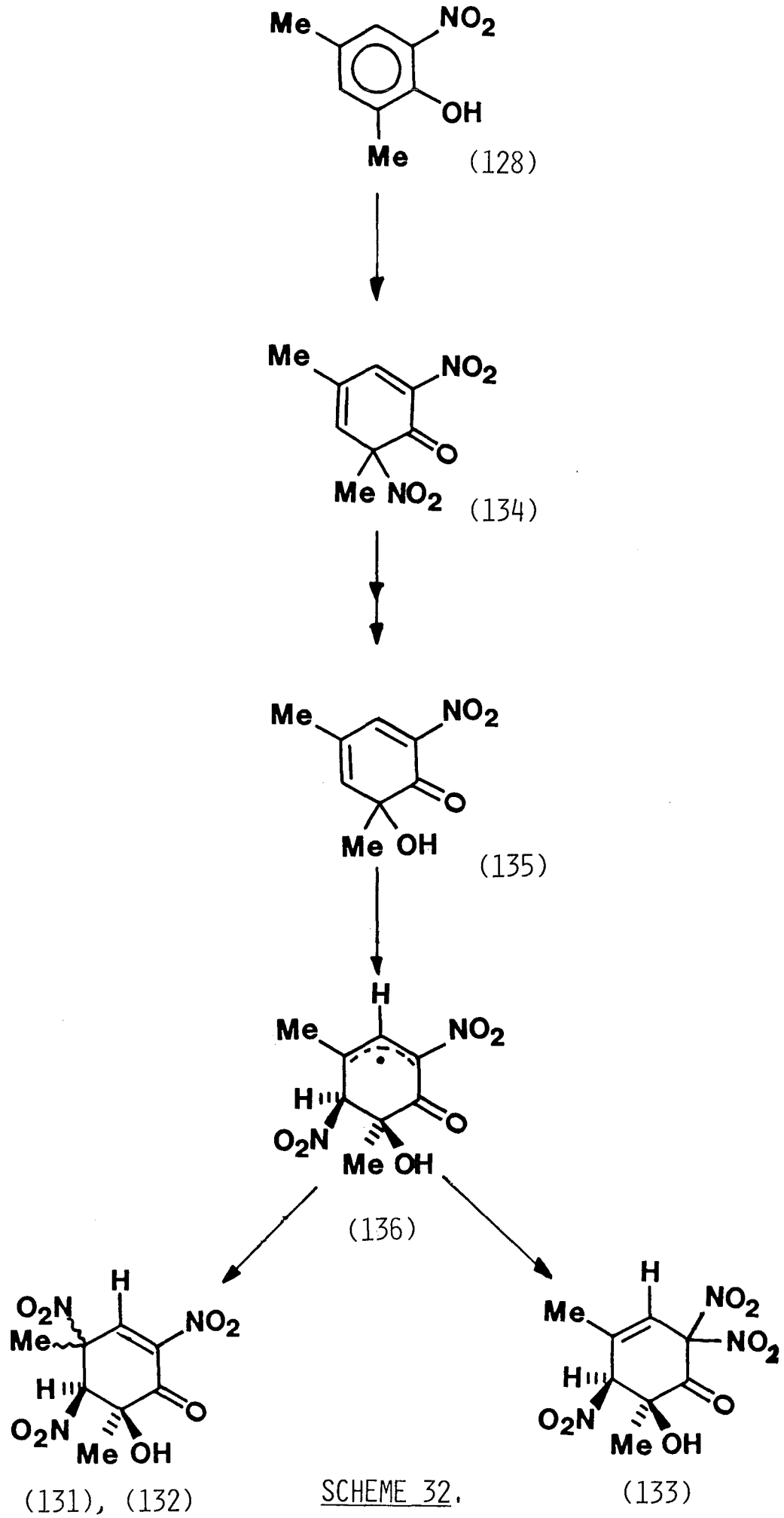


(123)

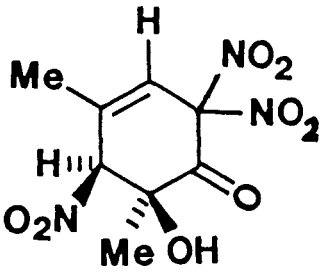
SCHEME 30


NO2
OH
Me
(122)
NO2
O
Me NO2
(125)
NO2
O
Me OH
(126)
≡
O···H
O
O2N
Me
H
NO2
H
O2N
O
Me OH
(127)
H
O2N
NO2
H
O2N
O
Me OH
(123)

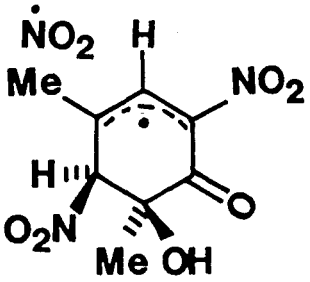
SCHEME 31.


Me
NO2
OH
Me
(128)
Me
NO2
O
Me NO2
(134)
Me
NO2
O
Me OH
(135)
H
Me
NO2
H
O2N
O
Me OH
(136)
H
O2N
Me
NO2
H
O2N
O
Me OH
(131), (132)
H
Me
NO2
NO2
H
O2N
O
Me OH
(133)

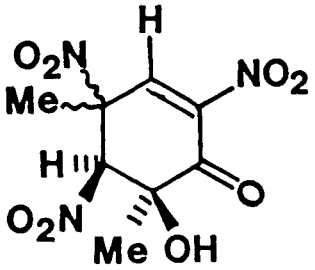
SCHEME 32.



(133)



(136)



(131), (132)

SCHEME 33.

ACKNOWLEDGEMENTS

I would like to express any gratitude to my supervisor, Professor Michael P. Hartshorn, for his encouragement and assistance throughout this work.

In addition, my thanks go to Dr Ward T. Robinson for assistance with the X-ray structure analysis work.

I would also like to thank the academic and technical staff of the University of Canterbury for their help and cooperation with special thanks to Karen Buckner for typing this thesis.

The award of a Teaching Assistantship (1982-1985) by the Chemistry Department, University of Canterbury, is also gratefully acknowledged.

Finally I would like to extend a special word of thanks to my family and friends for their support and encouragement.